MEDICATION ADHERENCE IN HIV-INFECTED ADULTS IN THE CURRENT ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

by

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Abstract

Background

Over the past decade, new and improved formulations of highly active antiretroviral therapy (HAART) have been introduced, which are easier to administer and may not necessitate high levels of adherence for HIV RNA suppression. At the same time, there has been an increase in the use of concomitant medications to treat chronic non-AIDS conditions (i.e., diabetes, hypertension) in HIV-infected persons. The goals of the dissertation were 1). to estimate the minimum cutoff of adherence to newer HAART needed for population HIV RNA suppression, 2). to determine whether this cutoff differed by specific regimen type, and 3). to determine if the increase in pill burden due to concomitant medication use impacted adherence to HAART.

Methods

We used data from three longitudinal cohort studies: the Multicenter AIDS Cohort Study (MACS), the AIDS Linked to Intravenous Experience (ALIVE), and the Veterans Aging Cohort Study Virtual Cohort (VACS) between 2001 and 2011, and analyzed them separately for this dissertation. Adherence was calculated from self-reported use in the MACS and ALIVE, and using pharmacy refill records in the VACS. In all three cohorts, the minimum needed adherence cutoff was defined as the level at which the odds of suppression was not significantly different than that observed with ≥95% adherence using repeated measures logistic regression. We controlled for confounding by indication using propensity score weighting. The effect of the number of concomitant medications on the minimum optimal adherence cutoff to HAART was also analyzed longitudinally using

repeated measures logistic regression models, and we further determined if this association varied by the pharmacologic class of the concomitant medication.

Results

In all three cohorts, there was an increase in the proportion with ≥95% adherence, and the proportion suppressed over time. Study 1 consisted of 1,006 HAART users with 10,971 person-visits in the MACS, and 197 HAART users with 1,745 person-visits in the ALIVE. In the MACS, levels of adherence between 80-84% were sufficient for HIV RNA suppression (OR (ref ≥95%): 1.43(0.61, 3.33)). In the ALIVE, we did not observe a minimum adherence cutoff below 95%. Study 2 consisted of 21,865 HAART users who contributed 82,217 person-years of follow-up. Suppression with <95% adherence was less likely ($p<0.05$) for PI-based regimens, whereas NNRTI users suppressed virus with lower adherence levels, odds ratios: 1.1 (0.89,1.36) and 0.82 (0.64,1.04) for 90-94% and 85-89% adherence, respectively. Study 3 consisted of 1,194 MACS participants contributing 11,678 person-years between 2001 and 2011, and 21,708 VACS patients contributing 79,972 person-years between 2001 and 2010. The use of concomitant medication increased over time in both cohorts, and the odds of achieving the minimum optimal adherence increased with an increase in the number of concomitant medications.

Conclusions

Despite the lower adherence level needed for suppression, HIV-infected persons should be instructed to achieve near-perfect levels of adherence. Providers should however not be reluctant to initiate HAART early in the infection, even to persons with historical barriers to adherence. Comprehensive counseling sessions and medication therapy management must be provided to optimize overall treatment outcomes in HIV-infected persons.

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CHAPTER ONE

Introduction

Overview and Specific Aims

Treatment complexity and side-effects are common barriers to adherence to HAART. New formulations of HAART are simpler and also have improved pharmacokinetic profiles, i.e., longer half-lives, and reduce the need for complete adherence. Owing to a decrease in AIDS-related mortality and improved life expectancy over the past decade, there has been an increase in non-AIDS-related morbidity and mortality, and consequently the use of concomitant medications for non-AIDS comorbidities.

This dissertation aims to evaluate the minimum level of adherence needed for HIV RNA suppression in the current HAART era, and determine if this minimum level of adherence is impacted by the increased use of concomitant medications for chronic non-AIDS comorbidities. Specifically,

Aim 1: To estimate the minimum optimal adherence level to HAART to achieve HIV RNA viral load suppression from 2001 through 2011.

Hypothesis 1a: Adherence to HAART has improved over time.

Hypothesis 1b: The minimum adherence level to achieve HIV RNA suppression has decreased over time.

Aim 2: To estimate the minimum optimal adherence level to HAART to achieve HIV RNA viral load suppression by HAART regimen type from 2001 through 2010.

Hypothesis 2a: The minimum adherence level to achieve HIV RNA suppression is different by HAART regimen type

Aim 3: To determine the association between HAART adherence and the number of concomitant medications used for chronic non-AIDS comorbidities among current HAART users on concomitant medications from 2006 to 2011.

Hypothesis 3a: The adherence to HAART decreases with an increase in the number of concomitant medications.

Background

Treatment of HIV Infection

Highly active antiretroviral therapy (HAART) was first introduced in 1996, and consisted then of a highly complex combination of antiretrovirals (ARV) which was difficult to administer owing to frequent dosing schedules and poor toxicity profiles.[1,2] Over the past decade, ARV formulations have become easy to administer, and have enhanced potency and toxicity profiles compared to their predecessors.[3,4,5] Based on the changing landscape of HAART, the treatment of HIV can be classified into 3 treatment eras (Figure 1.1): *the early HAART era (1996-2000)*, when treatment consisted of nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) or protease inhibitors (PI)-based regimens; *the mid HAART era (2001-2005)* when boosted PIs and newer classes like entry/fusion inhibitors were introduced, and the use of nonnucleoside reverse transcriptase inhibitor (NNRTI)- based regimens started gaining ground; *the current HAART era (2006 onward)*, when the first single fixed dose-combination drug Efavirenz (EFV)/Tenofovir (TDF)/Emtricitabine (FTC) was approved, second generation NNRTIs like Etravirine (ETV) were approved for use, and a new drug class Integrase Strand Transfer Inhibitors (INSTI)-based regimens was introduced.[6]

Currently, there are over 6 pharmacological classes and 30 ARVs approved by the FDA (Table 1.1). [6] According to current Department of Health and Human Services (DHHS) guidelines, "the optimal initial ARV regimen for a treatment-naive patient consists of two NRTIs in combination with a drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir (RTV), or an INSTI."[6] Initial HAART regimens are prescribed based on disease characteristics such as viral load and CD4 cell count.[6] Owing

to resistance, individual intolerance to medications, and potential drug-drug interactions, regimen changes are required. Among ART-naïve individuals, the median time to switching regimens is 8 months, and a recent study showed that 41% of HIV-infected persons switched their regimen within 5 years of treatment.[7]

Adherence to HAART

An integral component of the successful management of HIV, similar to that of other chronic illnesses, is a high level of adherence to treatment. Adherence to treatment is defined as "the extent to which patients take their medications as prescribed, starts with initiation of therapy, which occurs when the patient takes the first dose, and continues with the implementation of the dosing regimen, represented by the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen."[6,8] There is currently no gold standard measure for adherence in large population-based studies, but there are several validated tools available to use in different settings.[3,8,9] Adherence to HAART may be measured using direct methods such as measuring the drug levels in the blood, and indirect methods such as self-report, pill counts, pharmacy refills, and electronic monitoring devices. Table 1.2 shows the different methods used for assessing adherence to medication regimens, and their advantages and disadvantages for use.

In order to achieve and sustain viral load suppression, an adherence threshold of 95% was established as necessary.[10,11] Maintaining high levels of adherence over a long period of time is impaired due to numerous patient-, treatment- and disease-related factors. Virologic and immunologic outcomes, durability of responses, tolerability, drug-resistance, and pharmacokinetic factors vary at the individual level as well.[12] Barriers

associated with HAART adherence include side-effects, regimen complexity,[13,14] frequency of dosing, size of the pill, dietary considerations, and treatment cost.[15,16,17] Behavioral factors such as high-risk behaviors (i.e., use of non-prescription drugs), depression and other mental illnesses,[18,19,20] sociodemographic factors such as age, race, gender, and education,[21] and structural factors such as lack of social support, stigma, homelessness, poor access to treatment, incarceration, and lack of adherence counseling at the clinical setting also impact optimal adherence to HAART. [22,23,24,25]

As a consequence of needing to maintain a high optimal adherence threshold, providers may be discouraged from prescribing HAART universally to patients early in the infection due to potential barriers to sustaining high levels of adherence over time, in addition to potential acute and chronic complications of HAART.[26] Historically, HAART was initiated when the disease was symptomatic or at low levels of CD4 cell count.[27] Current guidelines recommend the use of HAART in all HIV-infected persons, irrespective of their CD4 cell count in order to prevent progression of the disease, and transmission of the infection to HIV-negative persons at risk.[6] They also state:

> "Regardless of CD4 count, the decision to initiate ART should always include consideration of a patient's comorbid conditions, his or her willingness and readiness to initiate therapy, and available resources. In settings where there are insufficient resources to initiate ART in all patients, treatment should be prioritized for patients with the following clinical conditions: pregnancy; CD4 count <200 cells/mm^3 or history of an AIDS-defining illness including HIV-associated dementia, HIV-associated nephropathy (HIVAN), or hepatitis B virus (HBV); and acute HIV infection."[6]

Providers therefore make the decision to initiate treatment based on other patient-related factors that may impact adherence to HAART.

For patients on HAART, maintaining long-term adherence requires significant time and resources.[28,29] This involves a multi-pronged approach starting with strengthening of the patient-provider relationship, ensuring linkage and retention in care, involving a multidisciplinary team (i.e., clinicians, pharmacists, nurses). An important component is educating the patient about HIV infection, HAART, and consequences of not adhering to treatment. Adherence monitoring, which typically involves patient interviews, patient diaries, as well as measurement of viral load, will not only enable the provider to learn how adherent the patient is, but also identify reasons for poor adherence.[30,31] Targeting specific barriers to adherence is the next step, which ranges from pill box organizers, and electronic reminders, to providing prescription drug coverage, and resource-intensive interventions to improve adherence.[32,33] Treatment adherence interventions include motivational interviews, community resources, administration of medications under supervised settings (e.g., Directly Administered Antiretroviral Therapy (DAART) for drug users), self-monitoring, regular counseling, incentives to improve clinic retention, and other adherence improvement strategies such as Sharing Medical Adherence Responsibilities Together (SMART for couples).[32,33,34] Although these interventions have been proven to be effective in improving adherence, they may not be beneficial in the long-term unless base-level infrastructural factors such as social support, income, insurance status, and homelessness are targeted. Providing the most optimal ARV regimen given individual barriers to treatment will be also cost-effective in the long run.

Minimum optimal adherence in the current era of treatment

In the current era of HIV treatment, with ease of administration of HAART, studies have shown that the use of once-daily HAART may enhance the overall adherence to treatment compared with twice-daily dosing.[13,35,36,37,38] Concomitantly, the improved pharmacokinetic profiles of second-generation formulations like boosted PI-based regimens (i.e., ritonavir-boosted atazanavir (ATV/r)), NNRTI-based regimens (i.e., rilpivirine (RPV) and etravirine (ETV)), and newer classes (i.e., INSTI-based regimens: raltegravir (RTG), elvitegravir (ETG)) have allowed for missing doses, and favorable treatment outcomes at moderate levels of adherence.[39] Table 1.1 shows the recommended HAART regimens in the current DHHS guidelines.

Although the recommended regimens have comparable efficacy, several factors that are taken into account in prescribing the most optimal regimen include safety considerations (i.e., adverse drug reactions, drug-drug interactions with concomitant medications), ease of administration (i.e., dosing frequency, number of pills, dietary requirements), the resistance profile, and the presence of comorbidities. Safety considerations vary for individual ARVs, and other concomitant medications which are administered. While NNRTI-based regimens are convenient to administer, boosted PI-based regimens have relatively low half-lives, and require frequent dosing.[6] The use of boosted PI-based regimens has however been suggested in persons with poor adherence owing to their improved potency and tolerability, and relatively high barrier for resistance.[6] In order to decrease the pharmacological activity of this class, several viral mutations are needed, and therefore, the prevalence of PI-based resistance is low.[6]

Further, virologic failure is relatively rare in persons with resistance to PI-based regimens.[6]

Given the intrinsic characteristics of specific HAART regimens, there is differing evidence regarding the levels of adherence needed for different HAART regimens. Maggiolo et al and Bangsberg[40] reported that moderate levels of adherence led to higher rates of viral suppression in NNRTI-treated patients compared with individuals receiving a single PI- or a boosted PI-based regimen. A later study by Chesney et al reported viral suppression for NNRTI-based regimens at adherence levels down to 55% to 75%.[14,41] However, a recent study by Genberg et al showed that non-adherence to NNRTI-based regimens was associated with worse outcomes compared to boosted PI-based regimens.[42]

While studies have shown that levels of adherence lower than 95% may be sufficient for viral load suppression, the minimum level of adherence needed for virologic suppression has not been established. Aim 1 attempts to fill this gap by determining a minimum optimal cutoff in the current era of treatment in two distinct risk groups. Further, since the adherence levels may vary by HAART regimen type, it is important to determine the levels of adherence specific to individual HAART regimens. Aim 2 determines whether the minimum optimal level of adherence is different by HAART regimen type.

Significance of a lower minimum optimal adherence cutoff

A report by the Institute of Medicine has stated that "increased focus on why people diagnosed with HIV fail to enter or remain in HIV care, as well as removing obstacles to care, such as by providing supportive services, will improve individual health

and reduce transmission of HIV to others."[43] A lower minimum optimal adherence cutoff to treatment will encourage providers to initiate treatment early in the infection, and also enable providers to focus attention on poor adherers and persons with barriers to treatment. The use of the most optimal regimen in persons with barriers to treatment adherence will help prevent drug resistance and virologic failure.

Aging, comorbidities, polypharmacy

The simplification and improved effectiveness of HAART has been accompanied by a decrease in AIDS-related morbidity and mortality, and longevity of HIV-infected persons.[44,45] Aging in HIV-infected persons is also accelerated as a result of inflammation and HAART-related side-effects.[46] As a consequence, polypharmacy is now increasingly prevalent in HIV-infected populations.

Polypharmacy, defined as the use of over 5 medications from different regimens, has led to treatment complexity in HIV-infected persons.[47] Some commonly used concomitant medications for non-AIDS conditions include antilipidemics, antihypertensives, oral hypoglycemics and antidepressants.[48,49] Polypharmacy has led to an increase in the total pill burden in HIV-infected patients.[50] There is strong evidence on the negative impact of pill burden on adherence to HAART.[13,14] However, there is limited data on whether the number of concomitant medications used for non-AIDS comorbidities impacts adherence to HAART. Moreover, this may likely vary depending on the use of particular HAART regimens, since the choice of the concomitant medication is often influenced by the HAART regimen type.[48] For instance, INSTI-based regimens are preferred over other regimens for coadministration with antidepressants

owing to potential drug-drug interactions between antidepressants and NNRTI-and PI-based regimens.

Age is a strong predictor of concomitant medication use, whereby older persons use more concomitant medications than younger persons.[49] Older persons are also better retained in care and adherent to their medications.[51] However, increase in the treatment complexity involves regular monitoring of potential drug-drug interactions and adverse events.[49,51] The presence of comorbidities like metabolic disorders and chronic kidney disease and the pathophysiology of aging itself may also impact overall drug pharmacodynamics, and reduce the efficacy of HAART.[52]

Therefore, the long-term use of concomitant medications for non-AIDS conditions is complicated, and may obscure the benefits of improved HAART formulations.[50] Identifying modifiable risk factors of adherence to HAART and concomitant medication use will provide targets for intervention. It will also help providers learn about factors impacting treatment management in the current HAART era. Aim 3 seeks to address this issue of increased treatment complexity as a result of concomitant medication use for chronic non-AIDS comorbidities, and its impact on adherence to HAART.

Conceptual framework and study variables

Figure 1.2 shows the conceptual framework for these investigations. Several factors at the individual level serve as predictors for adherence to HAART and HIV RNA suppression, including sociodemographic factors (i.e., age, race, sex, income, education, insurance status, marital status), behavioral factors (i.e., substance use, perception of

disease), structural factors (i.e., social support, access to care, incarceration, homelessness), comorbidities, concomitant medication use, and HIV disease indices, including virologic and immunologic outcomes. Achieving and maintaining high levels of adherence leads to viral load suppression. The minimum level of adherence needed to achieve viral load suppression is defined as the minimum optimal adherence. The type of HAART regimen prescribed is impacted by individual-level factors and treatment outcomes, and is a predictor of adherence to HAART and HIV RNA suppression. The number of concomitant medications used for chronic non-AIDS comorbidities is hypothesized to impact adherence to HAART, with more concomitant medication use leading to a decrease in adherence to HAART.

Study population and data sources

This dissertation uses data from three prospective cohort studies of HIV-infected persons in the United States. Table 1.3 provides a description of the different populations used for this dissertation. Aim 1 uses data from the Multicenter AIDS Cohort Study (MACS)[53] and the AIDS Linked to the Intravenous Experience (ALIVE)[54] study, which are both interval cohorts consisting of HIV- infected men-who-have-sex-with-men (MSM) and injection drug users (IDU) populations, respectively. Data are collected every six months using standardized questionnaires, blood collection and physical examinations. Self-reported clinical outcomes are confirmed by review of medical records. The MACS enrolled participants at four study sites across the country in Baltimore MD, Pittsburgh PA, Los Angeles CA, and Chicago IL. The ALIVE consists of one study site in Baltimore MD.

Aim 2 uses data from the Veterans Aging Cohort Study virtual cohort (VACS VC).[55] This cohort consists of administrative records, clinical data and pharmacy fill/refill records of HIV-infected persons presenting at a Veterans Health Administrative (VHA) site in the US. They were identified using electronic medical records based on a modified algorithm by Fasciano et al[56] to identify HIV-infected persons based on a combination of one inpatient and two outpatient ICD-9 diagnosis codes.

Aim 3 uses data from the MACS and the VACS VC cohorts.

Overview of this dissertation

This dissertation is organized into three publishable manuscripts representing Chapters 2, 3, and 4. Chapter 2 aims to examine trends in adherence to HAART and viral load suppression between 2001 and 2011, and determine the minimum optimal adherence to HAART in the current era of treatment in HIV-infected MSM and IDU older than 18 years in the US between 2006 and 2011 using data from the MACS and the ALIVE study.

Chapter 3 aims to examine trends in adherence to HAART and viral load suppression between 2001 and 2010, and determine the minimum optimal adherence to HAART in the current era of treatment for specific HAART regimen types in HIV-infected veterans older than 18 years in the US between 2006 and 2010 in the VACS VC.

Chapter 4 aims to determine the association between the number of concomitant medications used for chronic non-AIDS comorbidities in HIV-infected persons in the US older than 18 years, and using HAART since 2001 in the MACS and the VACS VC between 2006 and 2011.

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Table 1.1 FDA Approved HAART classes[6]

Pharmacologic class	Examples	DHHS guidelines recommended drugs	Characteristics
Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	*First generation drugs:* nevirapine (NVP), delaviridine (DLV), efavirenz (EFV) *Second generation drugs:* rilpivirne (RPV), etravirine (ETR)	EFV/TDF/FTC EFV/ABC/3TC RPV/TDF/FTC	- The single pill regimens are easy to administer - They have good virologic potency and durability - They have a low genetic barrier for the development of resistance especially in HAART-naïve patients
Protease Inhibitors (PI)	*Unboosted:* amprenavir (AMP), indinavir (IND), lopinavir (LPV), ritonavir (RTV), fosamprenavir, nelfinavir *Boosted:* ritonavir-boosted atazanavir (ATV/r), ritnonavir-boosted tipranavir (TPV/r) ritonavir-boosted darunavir (DRV/r)	ATV/r plus TDF/FTC DRV/r plus TDF/FTC ATV/r plus ABC/3TC LPV/r plus TDF/FTC LPV/r plus ABC/3TC	- They have good virologic potency and durability in treatment-naïve patients - They have the potential for significant drug-drug-interactions when administered with other concomitant medications owing to the inhibition of the cytochrome P (CYP) 450 enzyme - PIs are also associated with metabolic abnormalities
Integrase Strand Transfer Inhibitors (INSTI)	raltegravir (RAL) elvitegravir (EVG) dolutegravir (DTG)	RAL plus TDF/FTC DTG plus ABC/3TC DTG plus TDF/FTC	- INSTI-based regimens are recommended in HAART-

Pharmacologic class	Examples	DHHS guidelines recommended drugs	Characteristics
		EVG/cobi/TDF/FTC	naïve patients as they have few drug-drug interactions since it does not inhibit the CYP450 pathway - They require more frequent dosing and are administered twice daily
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)	lamivudine, zidovudine, emtricitabine, abacavir, tenofovir disoproxil fumarate, didanosine, dideoxyinosine, stavudine		
Entry/Fusion Inhibitors	maraviroc enfuviritide		

Table 1.2 Adherence measures[3,9]

Type	Adherence measure	Advantages	Disadvantages
Direct measures	Pharmacological and biochemical markers	They have higher reliability and validity compared to indirect measures.	It can be labor-intensive and costly to administer in the long run.
Indirect measures	Self-report (i.e., questionnaires, interviews, patient diaries)	They are cheap to administer, easy to collect, and used frequently in different settings.	They may be associated with recall error.
	Pharmacy refills	Adherence can be monitored over a long period of time and it is especially useful to study adherence for chronic medications. They are used frequently in different settings.	- They may misrepresent adherence as the medications may not be taken as prescribed. - They are not useful to monitor adherence over shorter periods.
	Pill count	They are feasible to use in day-to-day settings or clinical trials.	They are time-consuming and may misrepresent adherence as they do not measure if the patient took the medication as prescribed.
	MEMS cap	They provide a good representation of adherence and patient medication use patterns that may not be possible using other measures.	They are expensive and prone to malfunction and tampering.
	Electronic medical records	They can be used to monitor adherence over a period of time.	They can be inaccurate and hard to collect.

Table 1.3 Summary of study populations for dissertation

Design synopsis	Aim 1	Aim 2	Aim 3
Study population	HIV-infected persons in the MACS (N=1,006) and ALIVE (N=197)	HIV-positive persons in VACS VC (N=21,865)	HIV-infected persons in the MACS (N=1,194) and VACS VC (N=21,708)
Eligibility criteria	1. older than 18 years 2. on HAART between 2001 and 2011	1. older than 18 years 2. on HAART between 2001 and 2010	1. older than 18 years 2. on HAART between 2001 and 2011
Variables of interest *Exposure*	Adherence to HAART (self-reported)	Adherence to HAART (using pharmacy refill records)	Number of concomitant medications used for a chronic non-AIDS condition since the previous visit in the MACS or in a given year in the VACS
Outcome	HIV RNA suppression (<50 copies/mL)	HIV RNA suppression (<400 copies/mL)	Adherence to HAART (self-reported in the MACS and using pharmacy refill records in the VACS)
Potential confounders	sociodemographic and behavioral characteristics: age, race, annual income, insurance status, current injection drug use, non-injection drug use, current smoking, and moderate-heavy alcohol intake; treatment and disease characteristics: number of ARVs, CD4 cell count, and self-reported depressive symptoms (CESD>16)	sociodemographic and behavioral characteristics: age, race, geographical location, alcohol abuse, drug abuse, smoking; treatment and disease characteristics: HAART regimen type for a given patient in a year, depression diagnosis, CD4 cell count	sociodemographic and behavioral characteristics: age, race, geographical location, alcohol use, recreational drug use, smoking; treatment and disease characteristics: HAART regimen type for a given patient in a year, depression, CD4 cell count, HIV RNA Suppression,

Design synopsis	Aim 1	Aim 2	Aim 3
			VACS Risk Index, presence of a non-AIDS comorbidity

Figure 1.1 Mountain plot of HAART use over time [Source: Detels et al.][57]

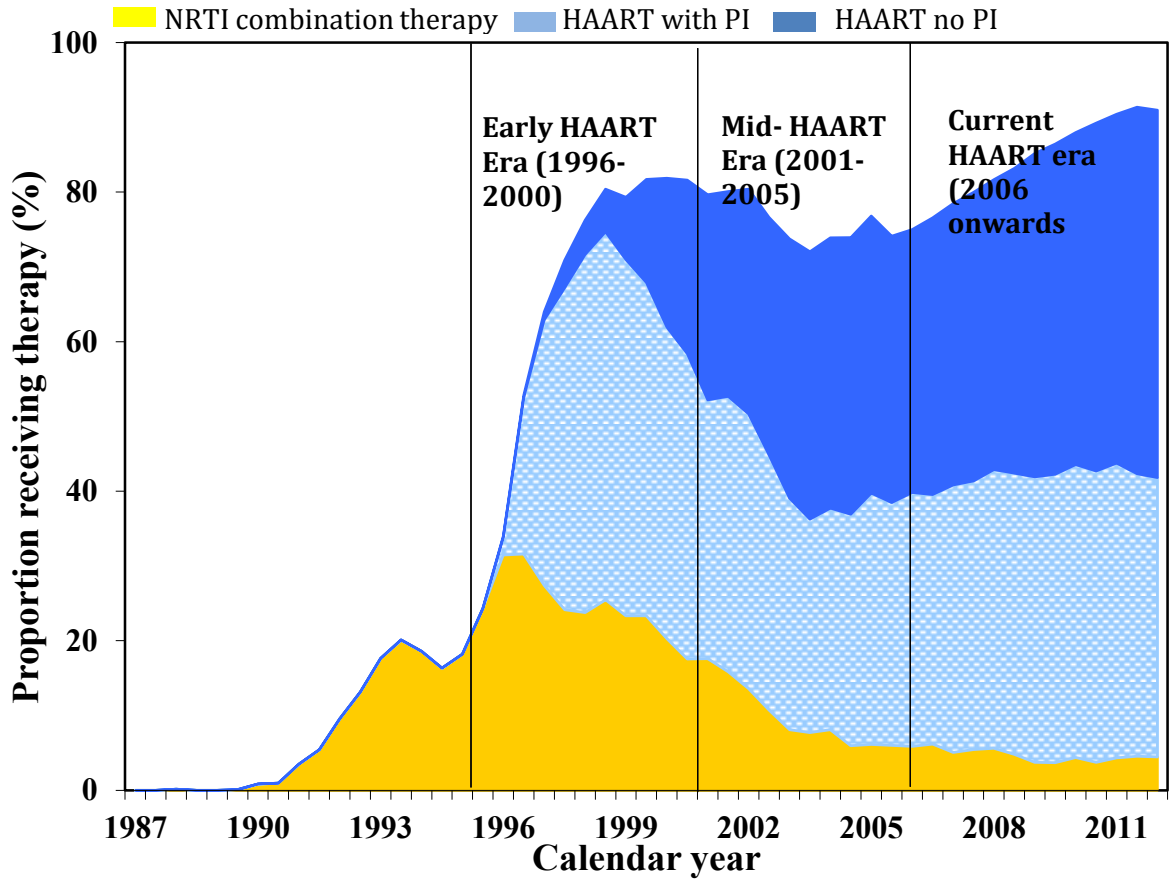
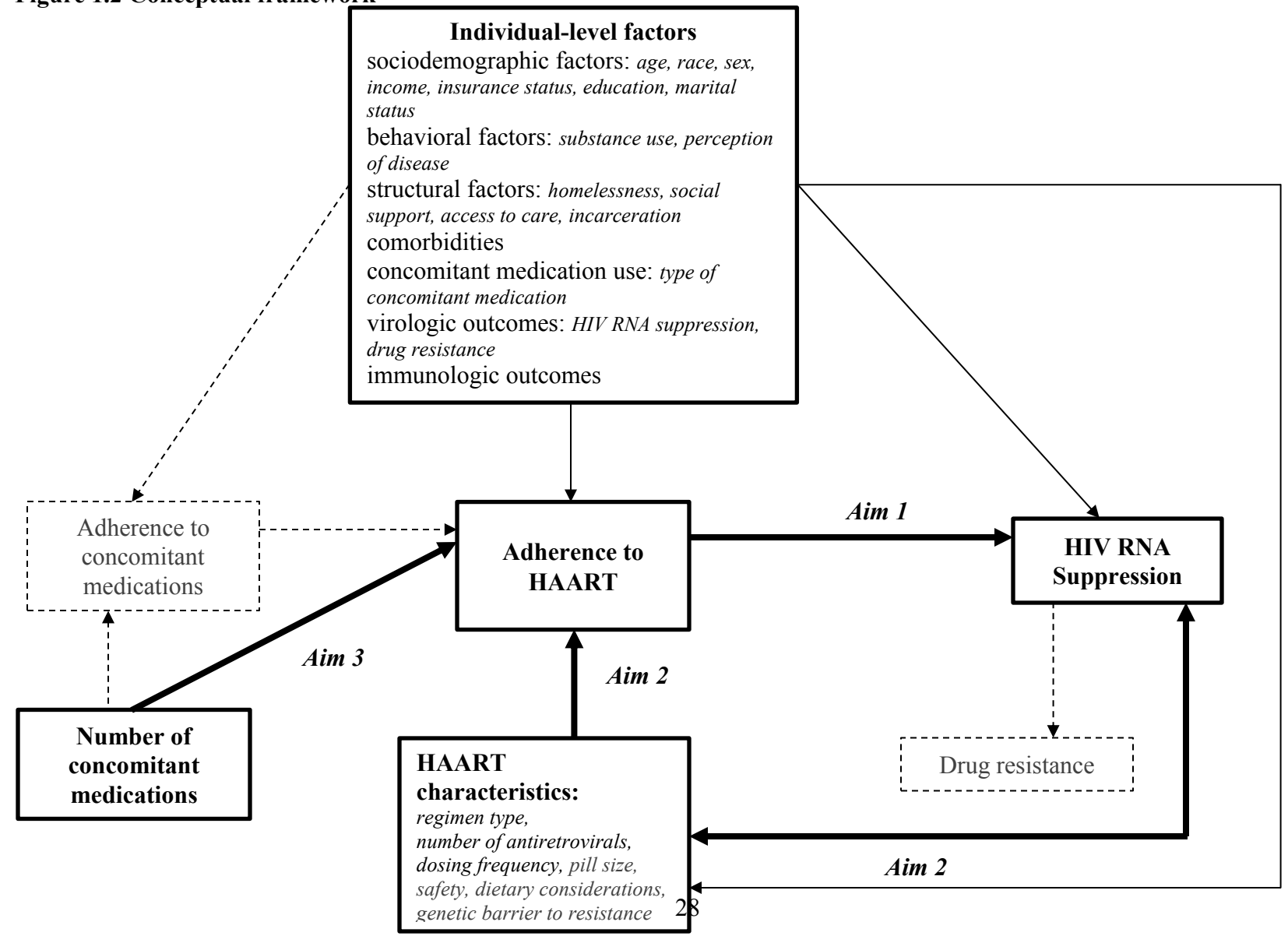


Figure 1.2 Conceptual framework



CHAPTER TWO

Level of adherence and HIV RNA suppression in the current era of Highly Active Antiretroviral Therapy (HAART)

Abstract

Adherence to highly active antiretroviral therapy (HAART) has been a barrier for universal administration at early stages of HIV, with ≥95% adherence deemed necessary for treatment effectiveness. Using longitudinal data from the Multicenter AIDS Cohort Study (MACS) and the AIDS Linked to the Intravenous Experience (ALIVE) study, cohort studies of men who have sex with men (MSM) and injection drug users (IDU), respectively, we determined whether self-reported adherence and HIV RNA suppression have changed between 2001 and 2011, concomitant with the availability of improved and simpler regimens. We further estimated the minimum adherence needed to achieve HIV RNA suppression in the population between 2006 and 2011, defining the cutoff as the level at which the odds of suppression was not significantly different than that observed with ≥95% adherence, and at which at least 80% were suppressed. In both cohorts, the proportion of HAART users reporting ≥95% adherence, and those suppressing HIV RNA improved over time. In the MACS, greater than 80% suppression was observed with 80-84% adherence and the odds ratio for suppression compared to those with ≥95% adherence was 1.43 (0.61, 3.33). In the ALIVE study, only 71.4% were suppressed among those who reported ≥95% adherence. While in a population of MSM HAART users on newer HAART regimens, being 80% adherent to treatment is sufficient for viral load suppression, it may be necessary for IDUs on older HAART regimens to be more than 95% adherent to HAART. Although all HIV-infected persons should be counseled to be 100% adherent, concerns related to non-adherence may be less of a barrier to initiation of modern HAART regimens early in HIV infection.

Background

Approximately 34 million people were living with HIV at the end of 2011.[1] With the introduction of highly active antiretroviral therapy (HAART) in 1996, there was a significant decline in AIDS-related mortality, and a longer life expectancy among HIV-infected persons treated with HAART.[2-6] The treatment of HIV has evolved over the past two decades from highly toxic, complex regimens, to newer formulations with improved pharmacokinetics that are easier to administer.[7] Effective treatment is defined by achieving low, undetectable plasma HIV RNA levels (copies/mL).[7] HAART needs to be administered daily over the course of a patient's lifetime in order to keep HIV RNA levels suppressed, decrease rates of resistance, and prevent progression to AIDS and HIV-related death.

Researchers investigating the effectiveness of HAART found that 95% adherence or better was necessary for approximately 80% of the population to achieve viral load suppression.[8,9] This high level of adherence has been challenging for many individuals due to barriers to adherence[7] that include treatment complexity,[10,11] patient-related high-risk behaviors such as use of non-prescription drugs, lack of social support, and sociodemographic factors such as age and comorbidities.[12] Individual responses to treatment such as tolerability, drug-resistance, durability of virologic and immunologic responses, and pharmacokinetic factors vary, and sometimes untreated symptoms due to suboptimal viral load suppression may impair subsequent adherence to HAART.[13] There are negative consequences of requiring high levels of adherence. First, physicians may be reluctant to prescribe HAART universally to patients early in the infection due to concerns about the ability to maintain adherence to HAART over time.[14] Second, for

patients on HAART, a significant amount of resources have been invested in improving adherence to HAART.[7] Resource-intensive strategies to improve HAART adherence have included electronic reminders, administration of medications under supervised settings, self-monitoring, counseling,[15] and adherence improvement strategies such as Directly Administered Antiretroviral Therapy (DAART)[16] for drug users, and Sharing Medical Adherence Responsibilities Together (SMART for couples).[16] In addition to the costs, these strategies are often administered only for fixed periods of time, and adherence to HAART and viral suppression may not be sustained after the strategies are withdrawn.[7,17]

Given the improved pharmacokinetics of newer HAART regimens over therapies administered in the earlier treatment era, and concerns about the need to maintain high adherence, empirical data are needed to know whether viral load suppression is possible at lower levels of adherence at the population level. A lower level of adherence required for effective treatment may alleviate the concerns noted above, result in earlier initiation of treatment in patients, and also enable physicians to determine which patients require in-depth counseling for adherence. Improving access to, and consistent use of medicines by HIV-infected individuals would decrease their risk of transmitting the virus to others, according to a recent report by the Institute of Medicine (IOM) on HIV treatment and quality of care.[18]

This study aimed to determine whether the association between adherence and HIV RNA suppression has changed over time, and to estimate the minimum optimal cutoff of adherence for HIV RNA suppression. The hypothesis was that the effectiveness of currently available HAART, measured by the suppression of HIV RNA to <50

copies/mL, does not require the near perfect levels of adherence (≥95%) as was required with earlier regimens.

Methods

We used longitudinal data collected prospectively between March 2001 and December 2011 from the participants in the Multicenter AIDS Cohort Study (MACS), and the AIDS Linked to the Intravenous Experience (ALIVE) study who reported using HAART between 2001 and 2011 for at least one visit.

The MACS is an ongoing prospective study of HIV-1 infection among men who have sex with men (MSM) in the United States.[19] A total of 6,992 men have been recruited since 1984 in 3 waves of recruitment: 5,622 men before 1991, 1,350 men in 2001-03, and 20 men since 2010, in Baltimore, MD, Chicago, IL, Los Angeles, CA, and Pittsburgh, PA.[19] Eligible persons had to be sexually active, 18 years or older, and free of an acquired immunodeficiency syndrome (AIDS)-defining illness, i.e., opportunistic infection or malignancy.[20] Every six months, the study visits entail physical examinations, collection of blood for concomitant laboratory testing and storage, and standardized interviews to collect information on demographics, medical history, and behaviors. MACS study protocols were approved by institutional review boards at each study center, and informed consent was obtained from all participants.

The ALIVE study is a prospective community-based cohort study of injection drug users (IDUs) in Baltimore, MD.[21] A total of 2,946 IDUs were recruited initially through community outreach in 1988-1989.[21] This was followed by three waves of recruitment in 1994-1995, 1998, and 2005-08, with a total of 1,067 participants being

followed over time since 1996.[17] Eligible persons had to be 18 years or older, free of AIDS during initial recruitment waves, and have a history of injection drug use. Similar to the MACS, at each 6-month study visit, researchers collect information on sociodemographic characteristics, medical history, HIV risk behaviors (sexual and drug-related), drug treatment, and collection of blood for concomitant laboratory testing and storage. ALIVE study procedures were reviewed and approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, and all participants provided written informed consent.

In both cohorts, HIV RNA levels were determined using the Roche Ultrasensitive RNA PCR assay (Hoffman-LaRoche, Nutley, NJ, U.S.A.) with a detection limit of 50 copies/ml, and CD4+ levels were quantified using standardized flow cytometry.[19, 21] The Baltimore MACS site and the ALIVE study use the same laboratory for flow cytometry and HIV RNA quantification.

Definition of HAART

HAART was defined using the DHHS guidelines as 'a combination antiretroviral treatment regimen containing at least 3 antiretroviral drugs - 2 nucleoside reverse-transcriptase inhibitor (NRTI) medications plus a protease inhibitor (PI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (INSTI)'.[22]

Based on the type of HAART regimen used in the general population, we classified the treatment of HIV into 3 eras: early HAART, 1996 through 2000; mid-

HAART, 2001 through 2005; and current HAART, 2006 through 2011. Date of HAART initiation was set as the visit date of the first HAART report.

Study population

Specifically, our study population was restricted to HIV-positive men and women who were on HAART from March 1, 2001 to December 31, 2011 (mid- and current eras). In addition, to examine trends in adherence and viral load over time, we further restricted the population to those contributing data from Jan 1, 2009 onwards. This latter restriction was implemented to avoid bias in temporal trends due to earlier attrition as a result of worse outcomes; for example, examining temporal trends by including those who developed AIDS and died before 2009, would result in different persons comprising calendar periods under study and bias the results. Only visits at which participants reported using HAART were included in the analysis.

Outcomes and Exposures

Adherence to HAART was defined using self-reported information collected at the study visits. In the MACS, the participant was asked about his actual use of each antiretroviral medication over the four days prior to the study visit. These responses were compared to the prescribed usage to determine adherence;

$$\frac{\text{Sum of the number of times the patient took the drug over a 4-day period}}{\text{Sum of the number of times they were expected to take the drug each day} * 4} * 100$$

As an exposure, adherence to HAART was treated as a categorical variable based on the distribution of adherence in the study population, and was also dichotomized as ≥95% or less. As an outcome, adherence was treated as a continuous variable. In the ALIVE study, self-reported adherence data were collected and the adherence percent was calculated similar to the MACS, except that usage over a 3-day period was ascertained.

Potential predictors of viral load suppression (<50 copies/mL) and adherence were sociodemographic and behavioral characteristics reported for the 6 months prior to when adherence and HIV RNA were measured. These included age, race, annual income (<$10,000 versus ≥$10,000), insurance status (private, public, none), current injection drug use, non-injection drug use (including cocaine, crystal methamphetamine, marijuana, heroin, poppers), current smoking, and moderate-heavy alcohol intake (defined as 3-4 drinks/day or more for more than once a month or ≥5 drinks/day for less than once a month) compared to lower quantities. Treatment and disease characteristics included number of antiretrovirals, CD4 cell count, and self-reported depressive symptoms (measured using the Centers for Epidemiologic Studies Depression Scale (CES-D)).[23] Persons with scores greater than 16 on the CES-D were classified as having symptoms of depression.[23] Both CD4 cell count and CES-D scores were lagged to the previous visit. In the ALIVE study, additional variables included homelessness, incarceration (≥1 week), and the length of the visit interval. We also controlled for the type of HAART regimen (NNRTI-based, PI-based, INSTI-based, and single pill) in both cohorts. Gaps in treatment were calculated for both cohorts since they were likely to impact the association between adherence and viral load suppression. Gaps in treatment were defined as not being on HAART for at least one visit since treatment was initiated.

In addition to being included as a confounder in the analysis, an interaction term between adherence and having one or more gaps in treatment was included to check for potential effect modification.

Statistical Methods

The 2 cohorts were analyzed separately since they represented two distinct risk groups (MSM and IDU), which could modify associations, and also because they presented with very different distributions of adherence. We restricted the analysis to person-visits with non-missing covariates, representing about 95% of the sample. Exclusion of these person-visits did not alter any trends or results from univariate analysis that used the full population. In both cohorts, for those with first HAART visits after 2006 with missing values in lagged CD4 cell counts, we used the CD4 count at that visit (MACS: 0.1%, ALIVE: 6.9%). The average change in adherence over time was determined at the population and individual levels. Linear mixed effects models with random intercept and slope, adjusted for confounders were used to study the effect of time on adherence. Adherence was modeled as a continuous outcome and two models were fit. In the first model, time was modeled as a dichotomous variable (<2006 and ≥ 2006), and in the second model, time was modeled as a discrete variable, using 2-year intervals. The fixed component of the model, the β coefficients, were used to determine the average change in adherence accounting for individual correlation between observations. The variance of the random slope, σ_2^2, estimated using maximum likelihood, was used to determine between-person changes over time. A likelihood ratio test was used to test if the random effects were significant.

To initially examine whether the proportion suppressing HIV RNA changed over time among those not fully adherent, we graphically depicted the proportion suppressed from 2001-2011 among those with <95% adherence. The best fit for the relationship between proportion suppressed and time was determined based on the Akaike Information Criterion (AIC) statistic. To define the minimum optimal adherence cutoff in the population, two criteria had to be met: 1) since historically, 80% of treated HIV-infected persons with ≥95% adherence had suppressed viral load,[8,9] this level had to be achieved; and 2) the odds of viral load suppression at the cutoff could not be statistically different from that observed in the population with ≥95% adherence. Since we were interested in defining this cutoff for adherence to current HAART regimens, we restricted this analysis to data from 2006 onwards. The proportion suppressed was plotted according to categories of adherence based on the observed distribution by cohort. Logistic regression models with viral load suppression as the outcome, and adherence percent as the primary exposure controlling for repeated measures over time and adjusting for confounders were used to compare the odds of suppression at the adherence category to that observed in the reference category (≥95% adherence).

All analyses were performed using SAS 9.2 (Cary, North Carolina, USA) and STATA 12.1 (College Station, Texas, USA). A p-value threshold of 0.05 was used to define statistical significance.

Results

Study Population

A total of 1,215 MACS participants contributed 12,310 person-visits, and 337 ALIVE participants contributed 2,188 person-visits in 2001-2011, of whom 1,026 and 197, respectively, contributed data since 2009. After excluding 5% of the person-visits due to missing covariates in the MACS, the study population consisted of 11,678 person-visits contributed by 1,194 participants, of which 1,006 were seen since 2009. The missing data by covariates were: alcohol use (1.8%), smoking (1.6%), non-injection drug use (1.9%), and depression (2.3%). Characteristics of the study populations seen since 2009 according to adherence are described in Table 2.1. Supplemental Table 2.1 shows the characteristics of all participants, compared to those seen since 2009. In the MACS, adherence was significantly associated with higher income, having private insurance, abstinence from injection and non-injection drug use, a higher CD4 count, and virologic suppression. In the ALIVE study, those with ≥95% adherence had a significantly lower proportion of alcohol users, and current injection and non-injection drug users. The overall proportion suppressed was also significantly higher for visits with ≥95% adherence compared to visits with <95% adherence.

In the MACS, the use of multiple pill regimens which were PI-based and NNRTI-based declined from 51% and 39%, respectively in 2006, to 36% and 16%, respectively in 2011. Concomitantly, the use of newer regimens –single pill, and INSTI-based has increased steeply over time from 5.7% and 0% in 2006 to 27% and 19% in 2011, respectively. In the ALIVE study, the use of PI-based and NNRTI-based regimens also declined from 70% and 23%, respectively in 2006, to 60% and 5%, respectively in 2011.

The use of single pill and INSTI-based regimens rose from 0% to the current use of 21% and 12% in 2011.

Adherence over time

As shown in Figure 2.1, the proportion reporting 100% adherence increased in both cohorts from 2001 through 2011. Restricting the population to those seen from 2009-2011, the increases in reporting 100% adherence from 2001-2011 was 84% to 90%, and 87% to 92% in the MACS and ALIVE study, respectively. Table 2.2 shows the results from linear mixed models used to examine the change in adherence over time. There was an increase in the average adherence over time in the MACS after accounting for within-person changes - an 11% increase in average adherence every two years, and a 33% increase in average adherence in the latter era compared to the earlier era. Adjusting for confounders attenuated the change in adherence over time in the population. There was significant variability (σ_2^2=3.3 (2.8, 3.9)) in the change of adherence over time. In the ALIVE study, there was a 14% increase in the average adherence every two years, and a 22% increase in the adherence in the latter era compared to the earlier era using the results from the adjusted model. There was significant variability in the change of adherence over time (σ_2^2=3.1 (1.3, 7.3)), and high variability in this trajectory in the ALIVE (Root Mean Square error: 11.69) as seen in Figure 2.1.

Almost 25% of HAART users in the MACS reported at least one gap in treatment and 12.9% reported multiple gaps of HAART such that HAART use was not reported for 7.7% of 13,339 person-visits following initiation. In the ALIVE, 73% of HAART users

reported at least one gap in treatment, and 53.4% reported multiple gaps such that HAART use was not reported for 34.6% of 3,426 person-visits following initiation.

HIV RNA suppression

Overall, 79.9% of the MACS person-visits had undetectable HIV RNA since 2001 (Supplemental Table 2.1), and the proportion suppressing HIV RNA in the MACS participants with <95% adherence increased since 2001, and ranged between 75% and 79% since 2006 (Figure 2.2). For the MACS, the model with time included as a piecewise linear term (AIC: 130.1) was a better fit than time modeled as a linear term (AIC: 138.2), or as a polynomial term (AIC: 139.2). For the ALIVE study, the model with time included as a linear term (AIC: 32.24) was a better fit than time modeled as a quadratic term (AIC: 33.74).

Minimum Optimal Adherence

In the current era (2006-11), the proportion suppressing HIV RNA increased with increasing adherence (Figure 2.3). At adherence levels between 80% and 84%, the proportion suppressing HIV RNA was greater than 80% (83.5%). For those with ≥95% adherence, 85.1% had undetectable HIV RNA levels. Random-effects logistic regression models with viral load suppression as outcome, adjusted for age, number of drugs, recreational non-injection drug use, alcohol use, race, smoking, lagged CD4 cell count, and type of HAART, confirmed that at adherence levels between 80% and 84%, the odds of viral load suppression were not significantly different than that among those with adherence levels ≥95%. Although HIV RNA suppression was significantly less likely

among those with a gap in treatment (OR: 0.61 (0.55, 0.67)), there was no statistically significant interaction between adherence and having at least one gap in treatment.

In the ALIVE study, we did not observe a minimum optimal adherence cutoff below 95% because less than 80% of the population was suppressed among those with ≥95% adherence (71.4%). Further, the adjusted odds of viral load suppression were appreciably lower with levels of adherence <95%, compared to the odds of viral load suppression at ≥95% adherence, although not statistically significant. Among those reporting ≥95% adherence, those who were currently injecting drugs were less likely to suppress HIV RNA than those not injecting drugs (55.4% vs. 74.8%, P<0.001). Similar to that seen in the MACS, the odds of suppression was significantly lower among those with a gap in treatment (OR: 0.50 (0.36, 0.69)), and there was no statistically significant interaction between adherence and having at least one gap in treatment.

Discussion

In these prospective cohorts of HIV-infected MSM and IDUs, there was an observable increase in the proportion reporting ≥95% adherence to HAART between 2001 and 2011. Our data are consistent with the hypothesis that adherence to HAART has become easier over time with newer and simpler HAART formulations. This concurs with previous studies reporting increased ease of adherence to once-daily regimens compared to multi-dose regimens.[13,24,25] Both cohorts reported an increase in the use of single pill regimens since 2006 (MACS: 5.7% to 27.2%, ALIVE: 0 to 21.4%, in 2011).

Newer drugs have also made viral load suppression possible at adherence levels lower than the 95%. Second-generation PIs (e.g., darunavir and tipranavir), NNRTIs (e.g., rilpivirine, etravirine), and newer classes such as INSTIs (e.g., raltegravir), enable durable viral load suppression with generally easier administration owing to high potency and improved pharmacokinetic profiles.[26,27] Importantly, they also have improved tolerability profiles, which may lead to better adherence. While newer HAART formulations may now be easier to administer, they also do not necessarily require consistently high levels of adherence for viral load suppression as suggested in previous studies.[26-28]

However, the population-level benefit of these newer formulations may be limited since some marginalized groups are not being prescribed these drugs as often as others. In our study, while more than 50% of MACS participants reported recent use of a newer HAART formulation, fewer than 35% of ALIVE participants were on these HAART regimens in 2011. This finding is consistent with a previous study by Mehta et al which reported that IDUs in Baltimore were initiating care at more advanced disease stages, and were not receiving newer HAART regimens.[29] The low proportion of suppressed visits in the ALIVE may thus in part be attributed to drawbacks of using older HAART regimens with shorter half-lives, increased pill burden, poor tolerability and drug resistance. However, it is also likely that the observation of a lower overall viral load suppression rate in the ALIVE study reflected a higher frequency of treatment gaps and greater barriers to consistent HAART use including frequent homelessness, incarceration, ongoing substance use, and more limited insurance. Discontinuous HAART use in this

population[21,30] may also have led to the development of drug resistance and subsequently higher rates of treatment failure.

Our data suggest that adherence levels as low as 80% to 84% may be sufficient for viral load suppression in populations using newer HAART formulations. This is consistent with literature suggesting that chronically ill patients using 80% of their medications, are generally categorized as being adherent to their treatment.[31] However, this message should be interpreted with caution. While our study points to lower adherence levels for effectiveness than previously established, the goal is not to encourage patients to be less adherent to medications. It is important for HIV providers to continue emphasizing the importance of 100% medication adherence. However, keeping in mind that some patients may not be as adherent to their medications due to specific barriers, they can divert resources for comprehensive counseling sessions towards patients with barriers to adherence.

Important predictors of high adherence to HAART and viral load suppression in the MSM cohort were found to be older age, non-Black race, higher CD4 count, and non-use of alcohol, cigarettes or recreational non-injection drugs, consistent with previous studies evaluating predictors of adherence to HAART in the MACS, and in other populations.[10,21,32-34] Similarly, in the ALIVE study, older age, non-use of alcohol, cigarettes, recreational injection and non-injection drugs, and not being incarcerated, were shown to predict high adherence, consistent with other studies of HIV-infected IDUs.[35-37]

As stated earlier, it was not possible for us to confirm a minimum optimal adherence cutoff lower than 95% for IDUs in the ALIVE. Although the lack of statistical significance in ORs could be attributed to the small sample size, only 71.4% were suppressed among those with ≥95% adherence, which is less than optimal, and lower, when compared to that observed in previous literature.[8] In addition to use of older regimens and low retention in treatment, this study population consisted of low-income individuals with a high proportion of substance use. When stratified by current injection drug use, significant differences were observed in the proportion of individuals suppressed at ≥95% adherence. Therefore, rate-limiting steps to achieving optimal adherence in this population may be patient-related behaviors, in addition to physician prescribing behaviors.

The use of self-reported adherence is a limitation to the study. Self-reported adherence is associated with recall error and social-desirability bias, which may lead participants to over-estimate their actual adherence.[34] Additionally, self-reported adherence may be less reliable in a population of IDUs.[38] This may have led to the relatively low proportion of suppression among those reporting ≥95% adherence in the ALIVE study. Another possible explanation for the lower level of suppression achieved by adherent ALIVE participants may be drug resistance. However, these data were not available. Another limitation may be misclassification of the antiretroviral medications used by the participants. Although cross-checking with medical records would address the reliability of self-report, it would not assess the validity of the actual use. Given that caveat, an earlier study in the MACS did show high agreement between self-reported and prescribed medication use.[39]

There were several strengths associated with this study as well. Both the MACS and the ALIVE are long-standing cohort studies examining the natural and treated histories of HIV in two important risk groups in the United States – MSM and IDU – that use standardized methods for data collection, and have relatively low attrition. Although self-reported data for adherence are associated with biases as described earlier, an important strength of our data is that persons were not reporting their adherence to their providers. This may have decreased the social desirability bias to some extent, since providers are more likely to counsel patients with sub-optimal adherence, and make changes to their treatment regimen. Participants reported their adherence before their viral load test, and therefore, in addition to temporality of the relationship, there was no bias in the reporting of adherence due to knowing the HIV RNA test outcome.

Conclusion

In summary, in the current era of HIV treatment, in addition to the ease of use of newer formulations which make high levels of adherence easy to achieve, improved formulations have made viral load suppression possible at lower adherence levels, which is consistent with evidence from recent studies.[7,40] While in a population of MSM HAART users on newer HAART regimens, being 80% adherent to treatment may be sufficient for viral load suppression, IDUs on older HAART regimens may need to be more than 95% adherent to HAART. In a population with more limited access and poorer engagement in care, the prescription of newer drugs may potentially help alleviate the barriers to treatment, and improve overall treatment outcomes. Future studies should aim to determine whether adherence and viral load suppression among IDUs may be

similar to that observed in the MSM population if given the same opportunity for newer regimens.

HIV providers should therefore not let concerns regarding adherence assume primacy and hinder the appropriate use of modern HAART regimens broadly at earlier stages of HIV disease. In parallel, retention and engagement in care should continue to be a primary objective, and this together with more universal prescribing patterns, will potentially improve individual outcomes and indirectly alleviate disease burden in the population. While HIV providers should continue to urge patients to achieve perfect adherence, comprehensive adherence counseling support may be best targeted to persons with more limited engagement in care and those dealing with substance use.

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Table 2.1. Study population characteristics (2001-2011)[δ]

Characteristics	MACS (N person-visits[*]=10,971, N=1,006)			ALIVE (N person-visits[*]=1,745, N=197)		
	Adherence <95% (N person-visits= 1,275, N=516), %	**Adherence ≥95% (N person-visits= 9,696, N=998), %**	**P-value**	**Adherence <95% (N person-visits= 197, N=95), %**	**Adherence ≥95% (N person-visits= 1,548, N=193), %**	**P-value**
Age, mean (SD)	47.6 (8.4)	49.4 (8.7)	*<0.01*	48.9 (6.1)	49.9 (6.6)	0.06
Black	33.5	24.8	*<0.01*	96.5	95.9	0.49
Male	100		-	69.0	67.8	0.78
Income						
≤$10,000	24.7	20.0	*<0.01*	93.4	90.5	0.19
>$10,000	75.3	80.0		6.6	9.5	
Insurance status[¶]						
Private	61.1	66.1	*<0.05*	6.6	8.1	0.47
Public	46.3	42.9	*<0.05*	82.3	77.6	0.14
None	9.6	6.6	*<0.01*	4.1	5.3	0.45
Current smoking[#]	32.0	30.3	0.20	79.2	75.6	0.35
Alcohol consumption[&]	15.0	13.5	0.20	46.7	32.4	*<0.01*
Current injection drug use	2.8	1.6	*0.01*	32.0	17.4	*<0.01*
Non-injecting recreational drug use	54.1	47.0	*<0.01*	26.4	17.8	*<0.01*
CD4 count at visit (cells/mm^3), mean (SD)	570.2 (284.2)	593.3 (275.9)	*<0.05*	399.7 (311.4)	372.5 (231.0)	0.14

Characteristics	MACS (N person-visits[*]=10,971, N=1,006)			ALIVE (N person-visits[*]=1,745, N=197)		
	Adherence <95% (N person-visits= 1,275, N=516), %	**Adherence ≥95% (N person-visits= 9,696, N=998), %**	**P-value**	**Adherence <95% (N person-visits= 197, N=95), %**	**Adherence ≥95% (N person-visits= 1,548, N=193), %**	**P-value**
Viral load (% suppressed)	70.1	81.2	*<0.01*	52.8	67.2	*<0.01*
Depression status (%)^	23.3	20.6	0.03	37.8*	29.1*	*0.04*

[δ] Population restricted to participants seen since 2009; [&]MACS: moderate-to-heavy consumption, ALIVE: drank >1 day/week; ^CESD (≥16) *2006-2011; [#]Current smoking (including occasional smoking); [¶]public & private not mutually exclusive; Italics denotes statistical significance

Table 2.2. Change in adherence over time (2001-2011)

Model	Time	Unadjusted estimate	Unadjusted estimate	Adjusted estimate	Adjusted estimate
		MACS	ALIVE	MACS[&]	ALIVE[#]
Model 1: Mixed	Per 2- year interval	0.11 (-0.06, 0.27)	0.18 (-0.25, 0.61)	-0.03 (-0.22, 0.16)	0.14 (-0.35, 0.64)
Model 2: Mixed	2006-11 vs. 2001-05	0.33 (-0.14, 0.81)	0.39 (-0.96, 1.74)	0.05 (-0.47, 0.57)	0.22 (-1.26, 1.69)

[&]Adjusted for age, race, alcohol use, smoking, type of HAART, and non-injection drug use

[#]Adjusted for age, alcohol use, non-injection recreational drug use, injection drug use, smoking, and visit interval

Figure 2.1. Proportion reporting ≥95% adherence over time (2001-2011)

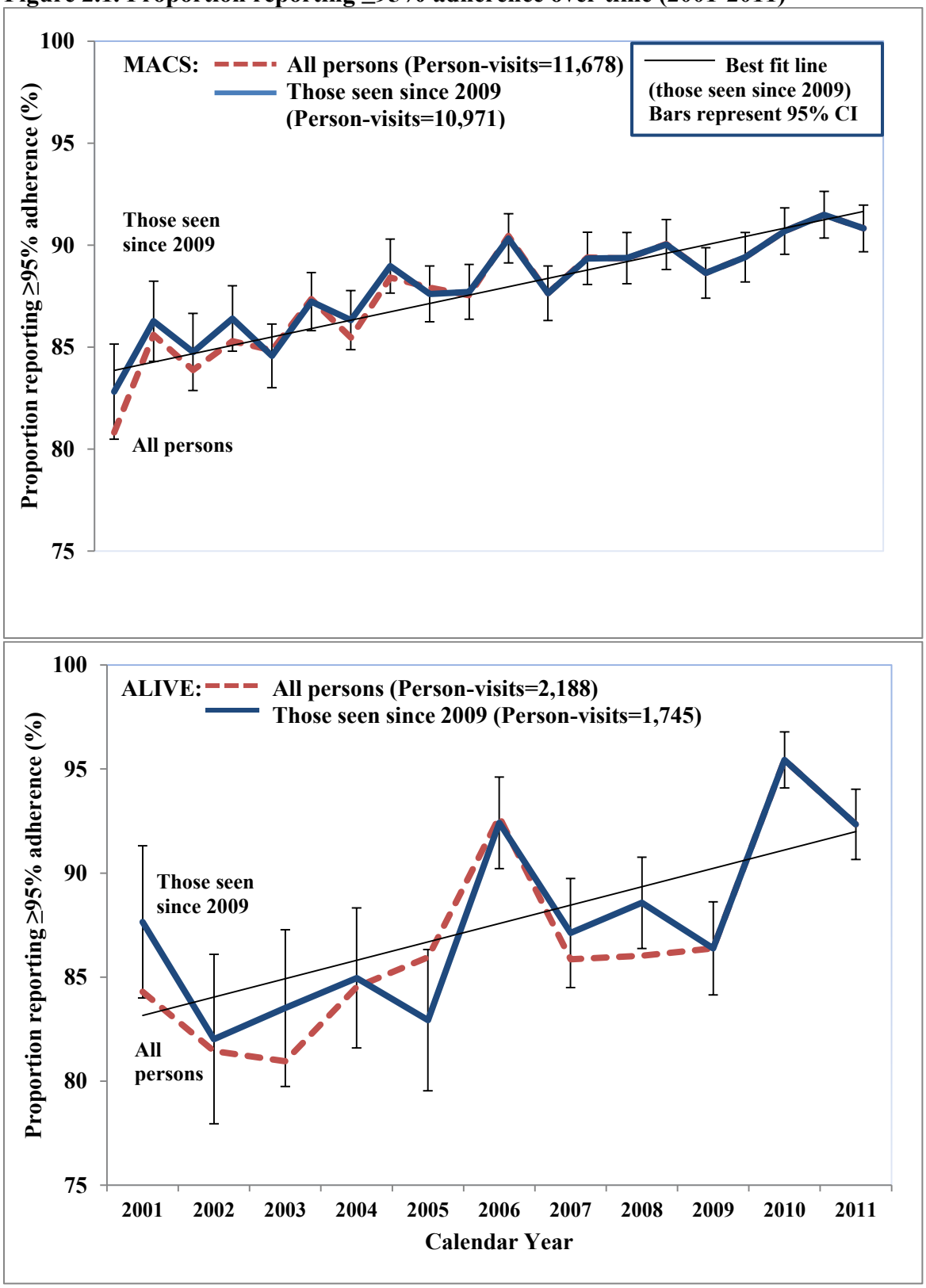


Figure 2.2 Proportion suppressing HIV RNA over time among participants with <95% adherence (2001-2011)

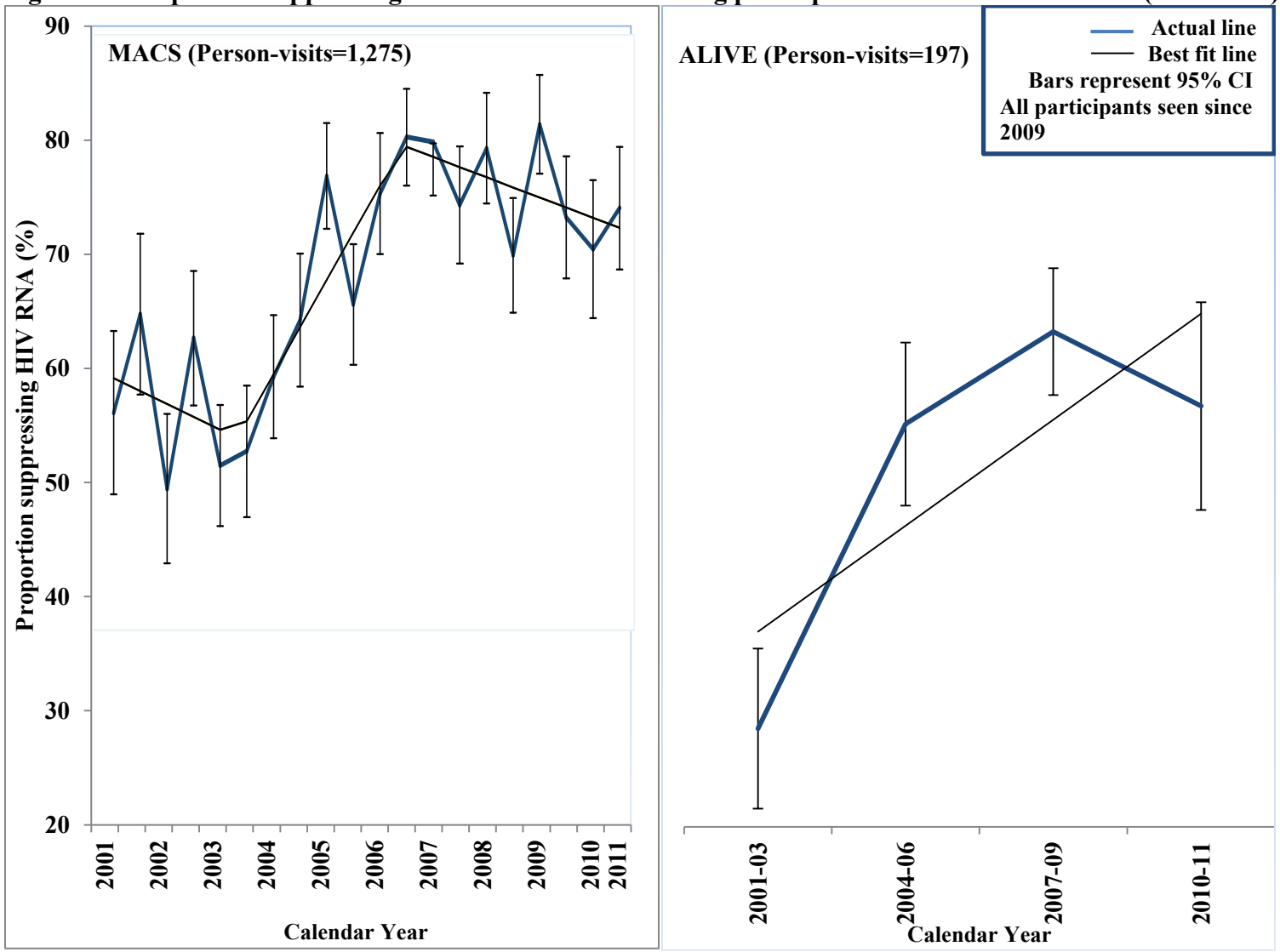
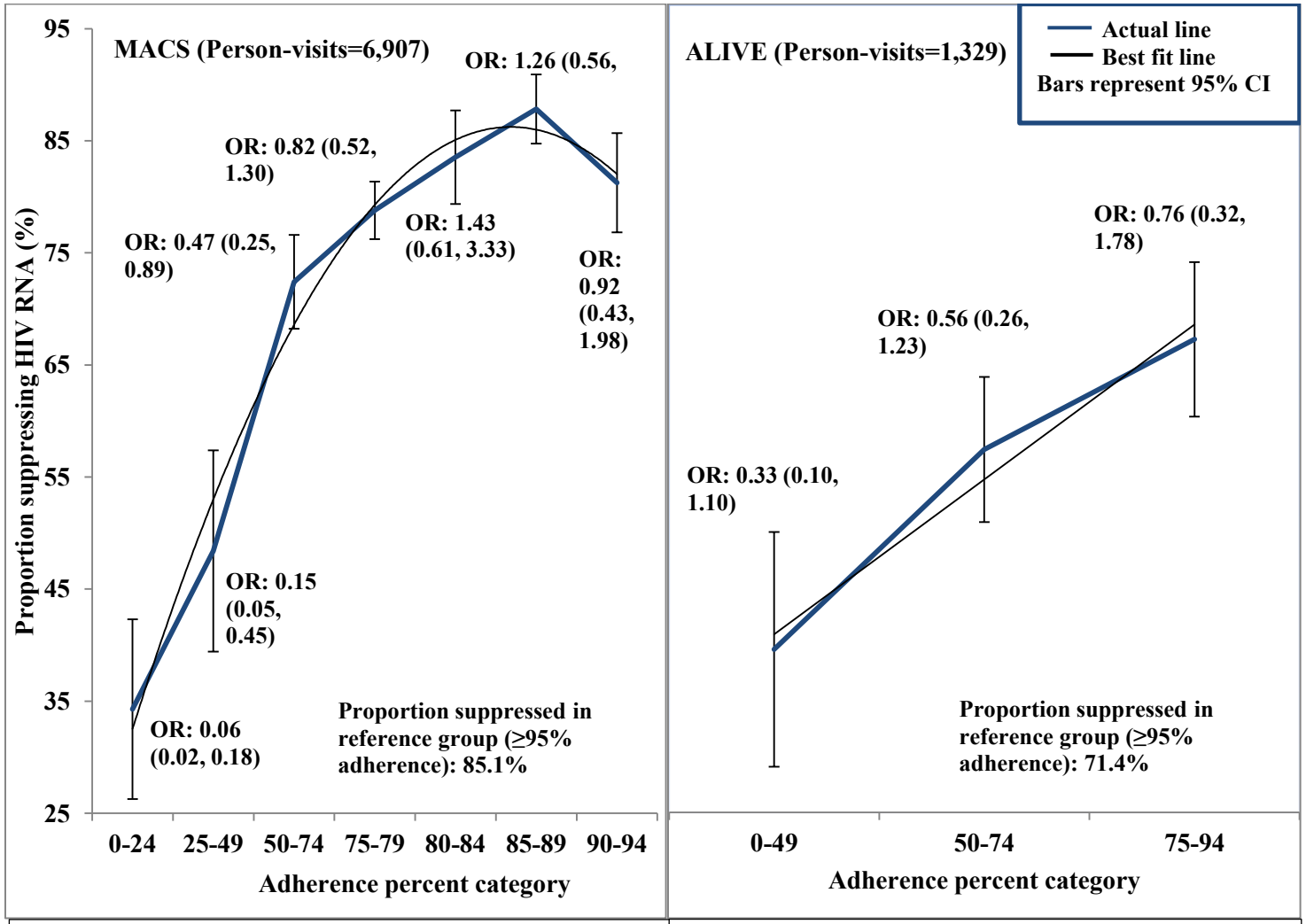


Figure 2.3. Proportion suppressing HIV RNA by HAART adherence category (2006-2011)



Odds Ratios for HIV RNA suppression obtained from a random-effects logistic regression model comparing suppression at the adherence category to adherence ≥95%, and adjusted for age, race, alcohol use, non-injection drug use, smoking, type of HAART, and CD4 count from previous visit

Odds Ratios for HIV RNA suppression obtained from a random-effects logistic regression model comparing suppression at the adherence category to adherence ≥95%, and adjusted for age, sex, injection drug use, alcohol use, smoking, CD4 count from previous visit, non-injection drug use, and type of HAART

Appendix Table 2.1. Study Population Characteristics (2001-2011): comparing everyone against those seen since 2009

Characteristics	MACS			ALIVE		
	All person-visits (Person-visits=11,678, N=1,194), %	**Those seen since 2009 (Person-visits=10,971, N=1,006), %**	**P-value**	**All person-visits (Person-visits=2,188, N=337), %**	**Those seen since 2009 (Person-visits=1,745, N=197), %**	**P-value**
Age, mean (SD)	49.1 (8.8)	49.2 (8.6)	0.26	49.4 (6.4)	49.8 (6.5)	0.05
Black	25.8	25.8	1.0	95.7	96.0	0.64
Male	100			67.7	67.8	0.94
Income						
≤$10,000	20.9	20.5	0.46	90.9	89.3	0.09
>$10,000	79.1	79.5		9.1	10.7	
Insurance status						
Private	64.8	65.6	0.26	7.0	7.9	0.28
Public	43.3	42.9	0.56	79.1	78.1	0.47
None	7.0	6.9	0.76	5.6	5.2	0.61
Current smoking[#]	31.0	30.5	0.41	75.8	76.0	0.88
Alcohol consumption[&]	13.7	13.7	1.0	33.2	34.0	0.60
Current injection drug use	1.8	1.7	0.57	20.5	19.0	0.24
Non-injecting recreational drug use	48.1	47.8	0.65	18.5	18.7	0.87
CD4 count at visit (cells/mm^3), mean (SD)	580.3 (279.6)	590.6 (277.0)	*<0.05*	361.5 (247.0)	375.5 (240.4)	0.25
Viral load suppression	78.3	79.9	*<0.05*	59.0	65.6	*<0.01*

Depression status^	21.3	20.9	0.46	30.3*	29.9*	0.82
Adherence %, mean (SD)	96.7 (11.5)	96.8 (11.4)	0.51	96.3 (12.3)	96.5 (12.1)	0.62

[&]MACS: moderate-to-heavy consumption, ALIVE: drank >1 day/week; ^ CESD (≥16) *2006-2011; [#]Current smoking (including occasional smoking); Italics denotes statistical significance

Appendix Table 2.2. Odds Ratios for viral load suppression at different adherence levels in the MACS (2006-2011)

Model	<25%	Between 25% and 49%	Between 50% and 74%	Between 75% and 79%	Between 80% and 84%	Between 85% and 89%	Between 90% and 94%
Crude	0.05 (0.02, 0.17)	0.15 (0.05, 0.46)	0.43 (0.23, 0.81)	0.74 (0.47, 1.17)	1.35 (0.58, 3.13)	1.40 (0.62, 3.16)	0.91 (0.42, 1.96)
Adjusted*	0.06 (0.02, 0.18)	0.15 (0.05, 0.45)	0.47 (0.25, 0.89)	0.82 (0.52, 1.30)	1.43 (0.61, 3.33)	1.26 (0.56, 2.84)	0.92 (0.43, 1.98)

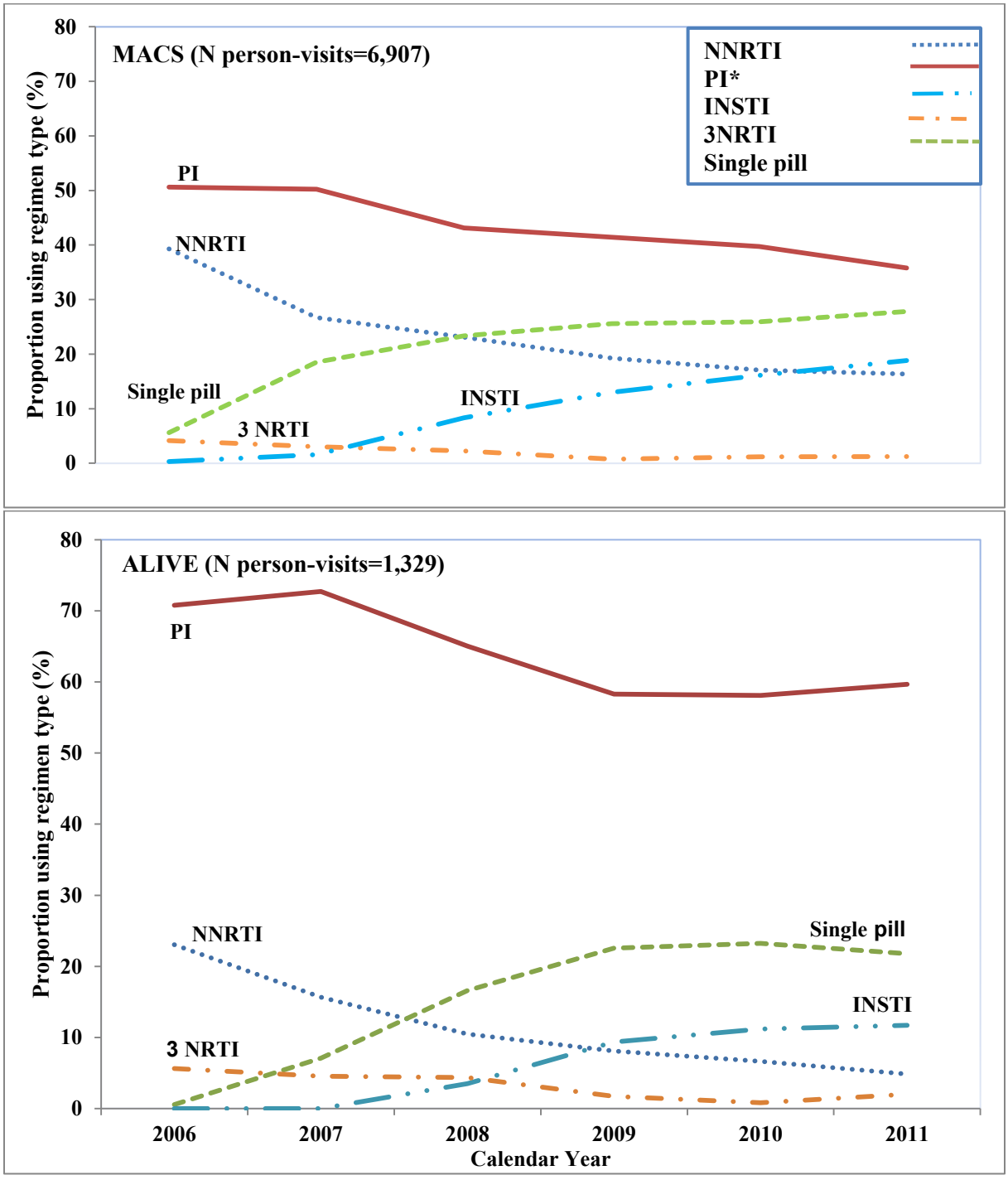
*Adjusted for adjusted for age, race, type of HAART, non-injection drug use, alcohol use, smoking, and CD4 count from previous visit

Appendix Table 2.3. Odds Ratios for viral load suppression at different adherence levels in the ALIVE study (2006-2011)

Model	Adherence <50%	Adherence between 50% & 74%	Adherence between 75% & 94%
Crude	0.26 (0.08, 0.89)	0.49 (0.22, 1.06)	0.80 (0.34, 1,88)
Adjusted*	0.33 (0.10, 1.10)	0.56 (0.26, 1.23)	0.76 (0.32, 1.78)

*Adjusted for age, gender, injection drug use, alcohol use, smoking, CD4 count from previous visit, non-injection drug use, and type of HAART

Appendix Figure 2.1. HAART regimen type by calendar year (2006-2011)



*Includes those with PI & NNRTI use (<10%)

CHAPTER THREE

Adherence and HIV RNA Suppression in the Current Era of Highly Active Antiretroviral Therapy (HAART)

Abstract

Background: We examined trends in adherence to highly active antiretroviral therapy (HAART) and HIV RNA suppression, and estimated the minimum cutoff of adherence to newer HAART formulations needed for HIV RNA suppression by regimen type.

Methods: We used VA pharmacy dispensing data from the Veterans Aging Cohort Study Virtual Cohort between October 2000 and September 2010, and defined adherence as the duration of time the patient had the medications available, relative to the total number of days between refills for all antiretrovirals in a year. Temporal trends in adherence and viral load suppression were examined by the patient's most frequently used HAART regimen in the year. The minimum needed adherence was defined as the level at which the odds of suppression was not significantly different than that observed with ≥95% adherence using repeated measures logistic regression.

Results: 21,865 HAART users contributed 82,217 person-years of follow-up. There was a significant increase ($p_{trend}<0.001$) in the proportion virally suppressed even among those with <95% adherence (2001: 38% to 2010: 84%) and the trend was similar when restricting to their first HAART regimen. For NNRTI multi-pill users, the odds of suppression did not differ for 85-89% adherence compared to those with ≥95% adherence, odds ratios: 0.82 (0.64,1.04), but for PI users, the odds of suppression significantly differed if adherence levels were <95% compared to ≥95% adherence.

Conclusions: Although all HIV-infected persons should be instructed to achieve perfect adherence, concerns of slightly lower adherence should not hinder prescribing new HAART regimens early in HIV infection.

Background

Over the past decade, the proportion of individuals on highly active antiretroviral therapy (HAART) who achieve HIV RNA suppression has increased dramatically.[1] This success has been attributed to improved medication adherence due to decreased HAART toxicity, fixed-dose combination pills, and simplified dosing strategies.[2,3]

With improved second-generation formulations of non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., rilpivirine, etravirine), protease inhibitors (PIs) (e.g., darunavir, atazanavir), and newer classes like integrase strand transfer inhibitors (INSTIs) (e.g., raltegravir), levels of adherence as those required with early HAART regimens (i.e., ≥95%),[4,5] may not be needed for maximal treatment effectiveness. A better understanding of the levels of adherence needed for effective treatment in the current era of HAART could further inform clinical care, and also alleviate provider concerns about prescribing HAART to patients with barriers to adherence at early stages of HIV infection.[6]

We sought to determine whether adherence to HAART and HIV RNA suppression have changed over time, and estimate the minimum optimal adherence level for HIV RNA suppression by HAART regimen type using data from a large, population-based cohort study.

Methods

Source population

The analysis used longitudinal pharmacy refill data collected prospectively from HIV-positive persons on HAART and followed in the Veterans Aging Cohort Study

Virtual Cohort (VACS VC) from October 1, 2000 to September 30, 2010. Details of the VACS VC have been previously described.[7] Laboratory and clinical data, and outpatient prescriptions for each subject were obtained by linking Immunology Case Registry, and Pharmacy Benefits Management Registry records, respectively.[8] HAART was defined using DHHS guidelines.[9] Only person-years in which HAART was used for at least 180 days in the year were included.

For each person-year, we used the regimen most frequently refilled to classify HAART as NNRTI-based, PI-based (including users of PIs, and both NNRTIs and PIs), INSTI-based, or 3 nucleoside reverse transcriptase inhibitors (NRTI) containing abacavir or tenofovir. We classified regimens as being single versus multi-pill, and whether administered once-daily versus twice-daily.

Outcomes and Exposures

Since HIV RNA levels were determined using assays with varying detection limits,[8] we used values of <400 copies/mL as suppressed viral load, and used the last HIV RNA test of the year for analyses. Sustained suppression was examined among those with multiple viral load measurements in a year and was defined as having undetectable levels following their first measurement if suppressed.

We calculated adherence to HAART using the medication possession ratio defined by Steiner and colleagues[10] which measures the duration of time the patient had the medications available, relative to the total number of days between refills. This was calculated for each person-year that contained at least one refill as follows:

$$\frac{\sum_{ARVs} Number\ of\ days\ supplied\ with\ drug\ in\ a\ year}{\sum_{ARVs} Total\ number\ of\ days\ between\ first\ and\ last\ refill} * 100$$

We excluded stockpilers (20.2% of study population), defined as person-years with a refill frequency exceeding the scheduled dosing interval by more than 5% since the Steiner algorithm was not validated in this subgroup.[8,11]

Potential confounders of viral load suppression and adherence included sociodemographic, behavioral, disease and treatment characteristics. Fixed characteristics included race, smoking, and geographical location obtained at the first time seen after October 1, 2000 (baseline). Time-varying factors included alcohol abuse, drug abuse, and major depression recorded using ICD-9 diagnosis codes, and for each year, the number of antiretrovirals used, number of days in possession of HAART regimens, regimen type, time since first HAART initiation, and mean CD4 cell count.

Statistical methods

We graphically depicted temporal trends of adherence, suppression, regimen type and dosing frequency from 2001-2010. The change in adherence over time was determined using linear mixed effects models with adherence percent as outcome, accounting for repeated measures over time, and adjusting for confounders. In sensitivity analysis, we restricted the population to: a). those who were in follow-up after Jan 1, 2009 (i.e., including those starting before or after 2009, but in follow-up between 2009 and 2010) to avoid a biased temporal trend due to earlier attrition of those with worse outcomes from low adherence, and b). the person-years on the first HAART regimen, since switching regimens may not be random, and may result from lower adherence and drug resistance.

We defined the minimum optimal adherence as the level of adherence at which the odds of suppression were not statistically different from that observed among those with ≥95% adherence. To focus on newer HAART regimens, we restricted this analysis to data from 2006 onwards and used logistic regression with viral load suppression as the outcome, and adherence percent as the primary exposure controlling for repeated measures over time and adjusting for confounders. Since characteristics informing prescribing patterns may affect adherence and HIV RNA suppression, we adjusted for this possible confounding by indication using propensity scores to weight the repeated measures logistic regression model. The propensity score for using an NNRTI-based regimen was determined by logistic regression which included age, race, geographical location, time since first HAART initiation, and CD4 count, HIV RNA suppression, drug abuse, alcohol abuse, and major depression diagnosis lagged to the previous year. Weights were generated as the average treatment effect for the treated (ATT), and included in the repeated measures logistic regression model as a covariate.

$$ATT,\ T = E[Y_i(1)-Y_i(0)|T_i=1];\ Y=\text{NNRTI use (yes=1 and no=0)}$$

In sensitivity analyses, we varied the restriction on the number of days on HAART in the year to 270 days and 330 days.

All analyses were performed using SAS 9.2 (Cary, North Carolina, USA) and STATA 12.1 (College Station, Texas, USA); p-value <0.05 was used to define statistical significance.

Results

Study population characteristics

A total of 21,865 HAART users contributed 82,217 person-years between October 1, 2000 and September 30, 2010. At baseline, the mean age was 45.7 (standard deviation (SD): 9.9) years, 98% were male, and 46.5%, 41.6%, and 7.6% were black, white and Hispanic, respectively (Table 3.1). Almost 60% were current smokers, 47% used VA facilities in the South, 23.3% in the Northeast, and less than 20% in the Midwest and West, respectively. Unadjusted, those with ≥95% adherence were older, less likely to have abused alcohol or drugs, and had higher CD4 cell counts compared to those with lower adherence during follow-up.

The use of PI-based and NNRTI-based multi-pill regimens declined between 2001 and 2010 from 65% to 43%, and 33% to 16%, respectively (Figure 3.1). Single pill regimen use and INSTI-based regimen use increased steeply since 2006 from 1% to 29%, and 0% to 11% respectively, in 2010. All the participants on single pill regimens were using efavirenz(EFV)/tenofovir disoproxil fumarate(TDF)/emtricitabine(FTC).

Adherence

The proportion of HAART users with ≥95% adherence increased marginally from 37% in 2001 to 42% in 2010 (Figure 3.2). More users of NNRTI-based regimens were ≥95% adherent than users of PI-based regimens. Up to 2006, multi-pill regimens were associated with significantly better adherence if taken once-daily versus twice-daily (Appendix Figure 3.1). From 2006 onwards, users of single pill regimens had better adherence than those using regimens comprised of multiple pills and doses. After

accounting for within-person correlation, there was a 13% increase in the adherence every two years on average (Appendix Table 3.1).

HIV RNA suppression

Among those with <95% adherence, the proportion suppressed increased over time from 38% in 2001 to 84% in 2010 (p_{trend}<0.001) (Figure 3.3A), and did not appreciably differ when restricted to persons seen since 2009 or on their first HAART regimen. This increase in viral suppression was observed even among those with 75-79% adherence (Figure 3.3B). Across all years, HAART users had an average of 3 HIV RNA tests per year, and the proportion with sustained viral load increased over time from 77.5% in 2001 to 92.0% in 2010. This trend occurred across regimen types but at different levels (Appendix Figure 3.2).

Minimum optimal adherence

Overall, HIV RNA suppression for persons with 90-94% adherence did not differ from those with ≥95% adherence (odds ratios (OR): 1.05 (0.91, 1.21)) (Appendix Table 3.2). However, the proportion suppressed among users of an NNRTI-based regimen was higher at all adherence levels compared to that among users of PI-based regimens (Figure 3.4). The significant (P<0.05) difference in the minimum optimal adherence by regimen type persisted even after adjusting for the propensity for using NNRTIs and therefore we used stratified analyses to identify treatment-specific cutoffs. Users of PI-based regimens were less likely to suppress virus if <95% adherent compared to ≥95% adherent (e.g., 90-94% adherence, OR: 0.88 (0.77, 0.99)) (Figure 3.5). Conversely, among NNRTI users,

the odds of HIV RNA suppression at adherence levels as low as 85% did not significantly differ compared to that with ≥95% adherence (OR: multi-pill users: 0.82 (0.64,1.04), single pill users: 0.88 (0.69, 1.11)). There were no differences in the proportions virally suppressed in NNRTI users with 90-94% adherence compared to ≥ 95% adherence (OR: 1.10 (0.89, 1.36)).

Sensitivity analyses by varying the number of days on HAART inclusion criterion, and restricting to the first HAART regimen did not alter our results appreciably (Appendix Figure 3.3, Table 3.3).

Discussion

In this population of HIV-infected treated persons seeking care at a Veterans Health Administration Center, adherence and viral load suppression improved between 2001 and 2010, concomitant with use of newer HAART regimens. The proportion suppressed increased over time even among those with less than perfect adherence. More of those using NNRTI-based regimens had adherence ≥95%, and also a higher proportion suppressed at lower levels of adherence compared to those using other regimens.

The utilization of newer HAART regimens in this study population is similar to that in other HIV-infected populations.[12] Single-pill use began in 2006, and rose to almost 30% in 2010. The higher adherence observed with the use of single pill regimens conforms with studies contrasting the ease of use of single pill regimens and once-daily formulations with multi-dose regimens.[12-17] and also with studies of medication use in the general population.[18] Lower toxicity profiles may also have contributed to improved adherence to newer drugs.

In addition to being easier to administer, newer HAART formulations do not necessitate consistently high levels of adherence for viral load suppression as required by older HAART formulations.[2,16] Second-generation drugs have enhanced pharmacokinetic profiles, lower toxicities and lower resistance rates, and lead to sustained viral load suppression.[2,19,20] Our finding of a higher proportion sustaining viral load suppression in the latter era compared to the earlier era is consonant with the improved effectiveness of the newer drugs. Although a relatively new formulation, INSTI-based regimens had a lower proportion suppressed over time compared to other regimens. This may be attributed to the fact that this was the first-line regimen for less than 1% of the study population; their initial use was therefore predominantly as a salvage regimen for patients with failed prior regimens, who were as a consequence, more prone to virologic failure.

Our data suggest that adherence levels lower than 95% may be sufficient for viral load suppression in populations using newer NNRTI formulations. Although based on relatively imprecise estimates (i.e., wide confidence intervals), 85-89% adherence on NNRTI-based regimens may be sufficient for viral load suppression; 82.2% of this group suppressed virus compared to 84.6% of those with ≥95% adherence. The inference of effective treatment with less than perfect adherence concurs with the literature suggesting that on the basis of pharmacy refill data, chronically ill patients using 80% of their medications are generally categorized as being adherent to their treatment.[21] While being 85% adherent to HAART may be sufficient for optimal virological outcomes in a population, we would like for this message to be interpreted with caution at the individual level. Several non-HAART related barriers such as treatment access, behavioral factors,

and comorbidities, may lead to sub-optimal adherence, resistance and treatment failure.[3] Providers must continue to encourage patients to achieve perfect adherence, but comprehensive adherence improvement strategies may be administered on a case-by-case basis.[22]

There were limitations in our study. We calculated adherence using pharmacy refill records, making the assumption that the medications were used as dispensed. While pharmacy refill records have the disadvantage that they may misrepresent adherence,[3] they are not associated with recall error and social-desirability bias as with other adherence measures like self-report and pill count.[3] Although our findings are generalizable due to the large sample size with a widespread geographical distribution in the US, extrapolating our findings to women is limited since our population was predominantly male. The population had a higher CD4 count on average, and a higher proportion suppressed while on HAART than some other studies,[23] and this may indicate different medication choices in this population. The generalizability of our findings is also limited due to the population being insured through the VA, indicating good access to care. The internal validity of our study is however boosted by this very fact since 98% of the participants do not refill their prescriptions outside of the VA.[24] Resistance data were not available, and hence we do not know if PI-based regimens were used preferentially among patients with known resistance or known poor adherence.

Despite the limitations, our study had several strengths. Over 20,000 HAART users were followed >10 years allowing us to reliably examine trends in adherence and viral load suppression, and determine the minimum adherence cutoff by HAART regimen type after controlling for potential confounding by indication. Our findings that NNRTI-

based regimens have relatively better adherence and virological outcomes will enrich research on adherence in the current era by focusing attention to very low adherers. These data also serve as a guide for providers treating HIV-infected persons.

An integral component of the treatment of HIV like other chronic illnesses is adherence. With newer HAART regimens, adherence is easier, and high adherence levels are not required for viral load suppression. Providers should not let concerns regarding barriers to adherence hinder the prescription of newer HAART regimens at early stages of the disease.[25] A recent report by the Institute of Medicine on HIV treatment and quality of care states that "improving access to, and consistent use of medicines by HIV-infected individuals would decrease their risk of transmitting the virus to others".[26] Efforts must be made to maximize the prescription and use of single pill regimens. Future work should focus on the use of other approved single pill regimens and newer drugs now included as recommended regimens in more recent guidelines, and their use in populations with poor access to and retention in care.

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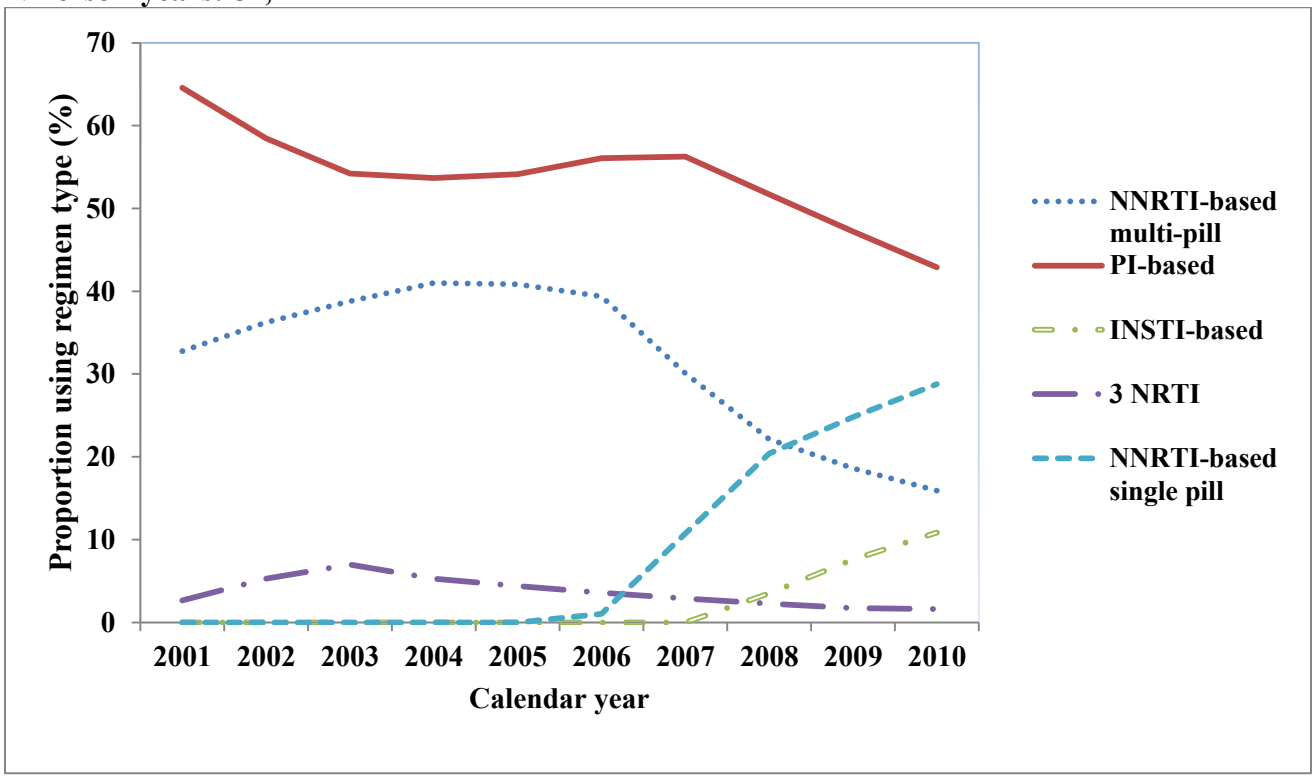
Table 3.1. Characteristics of study population (2001-2010)

Characteristics	Baseline N persons=21,865	Adherence <95% (N person-years= 48,662)	Adherence ≥ 95% (N person-years= 33,555)
Age, mean (SD)	45.7 (9.9)	51.9 (9.4)	53.6 (9.7)
Black (%)	46.6	49.3	38.0
Male (%)	98.0	97.9	98.3
Smoking at baseline (%)	57.2	58.6	48.4
Alcohol abuse (%)$^{\delta}$	10.5	9.8	6.3
Drug abuse (%)$^{\delta}$	13.4	13.1	8.1
Depression status (%)$^{\delta}$	7.7	7.5	6.9
CD4 count (cells/mm^3), mean (SD)	422.1 (265.5)	480.6 (281.6)	521.0 (277.8)
Geographical location (%)*			
Northeast	23.4	25.8	23.2
Midwest	13.8	12.7	14.1
South	46.5	46.6	44.6
West	16.3	14.9	18.0
Year 2006 onwards	35.9	57.5	60.5
Adherence at baseline, mean (SD)	87.6 (13.7)	N/A	N/A

*Northeast: CT, ME, MA, NH, NJ, NY, PA, MD, DC, DE, RI, VT; Midwest: IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; South: AL, AR, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV; West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; $^{\delta}$ Based on ICD-9 diagnosis codes

Figure 3.1. Regimen use over time (2001-2010)

N Person-years: 82,217



^NNRTI-based regimen excludes single pill regimen

Figure 3.2. Distribution of ≥95% adherence over time (2001-2010)

N person-years: 82,217

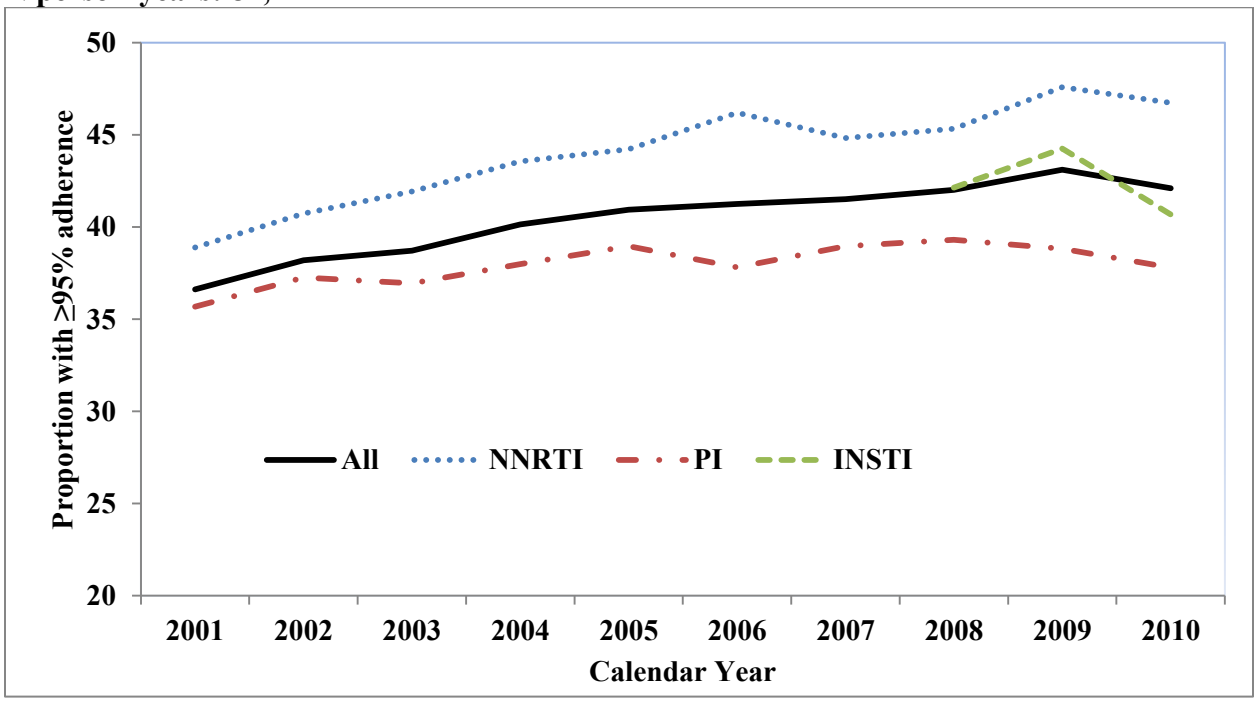


Figure 3.3. Proportion suppressed among those with <95% adherence (2001-2010)

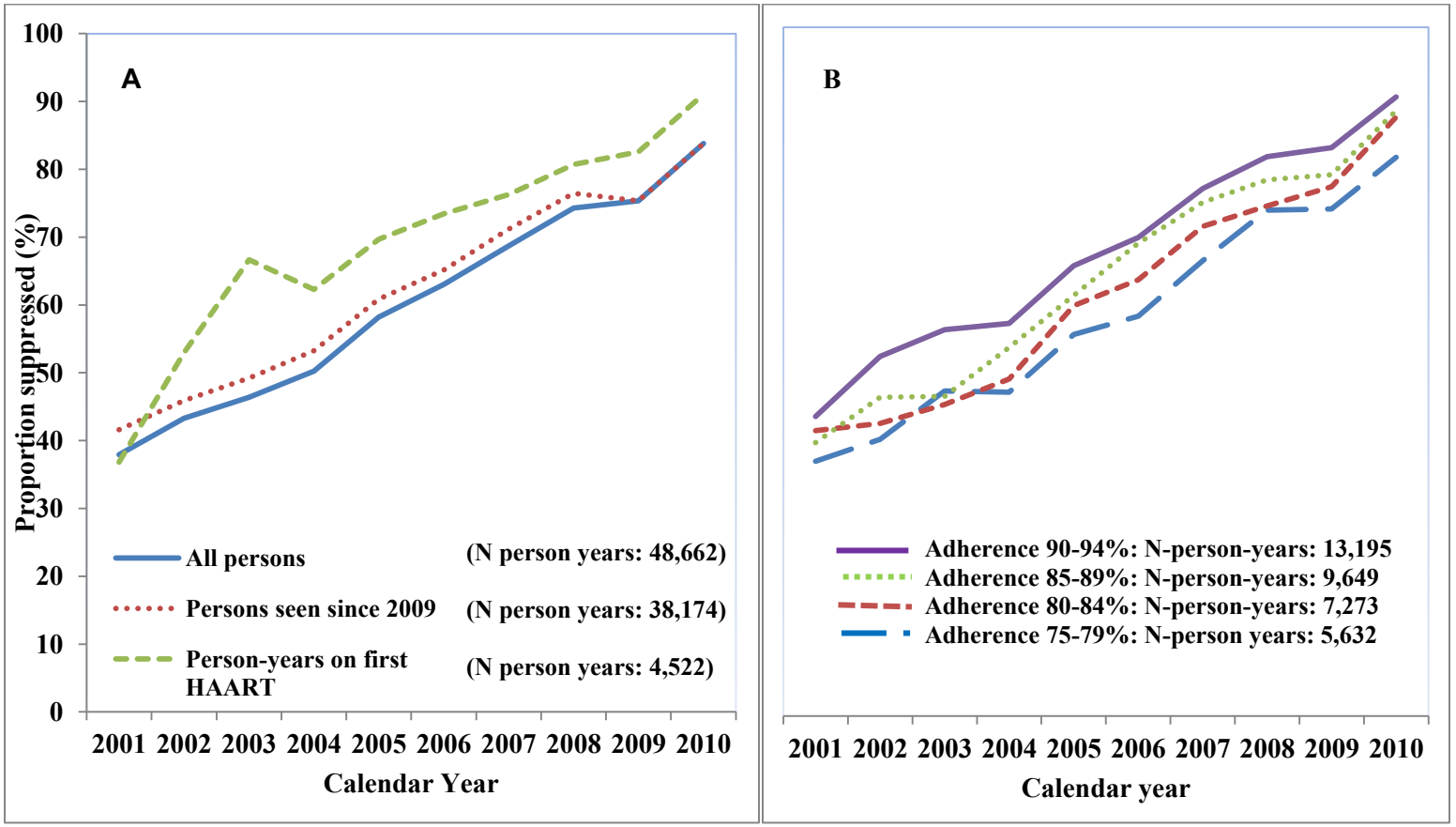
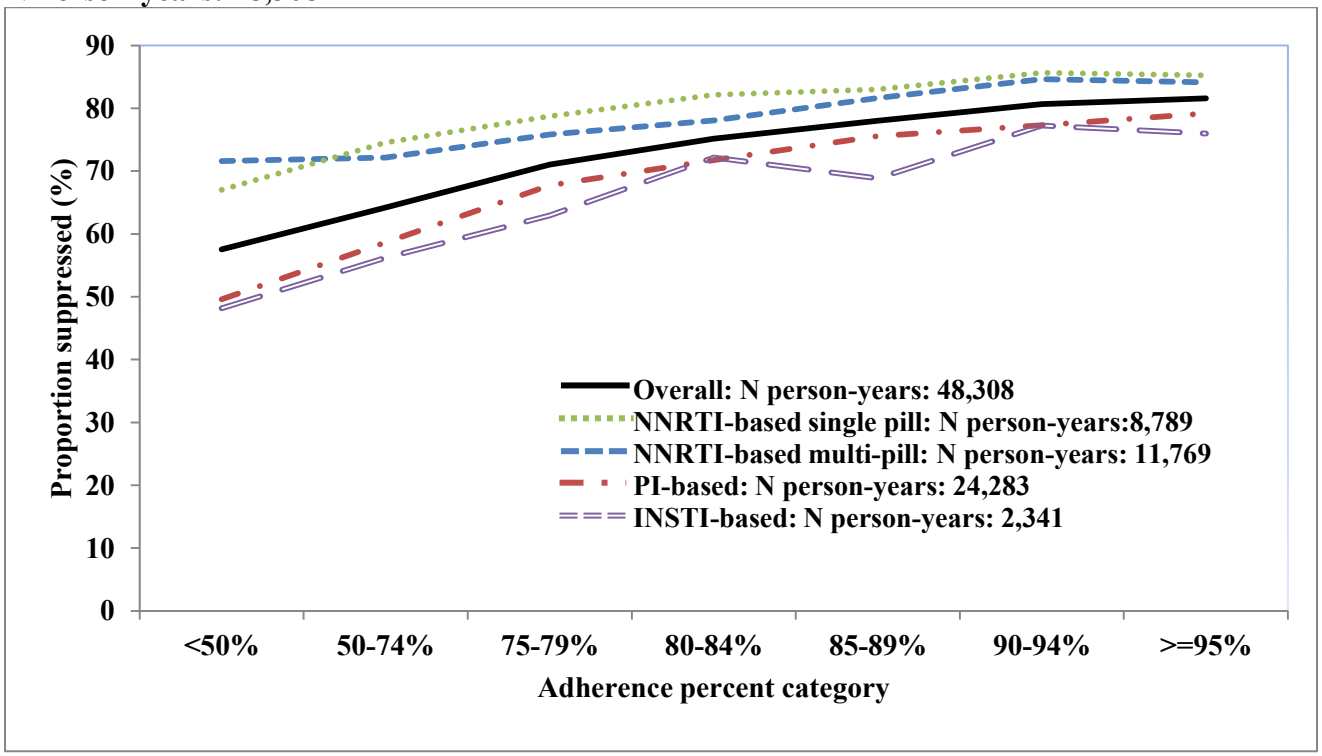


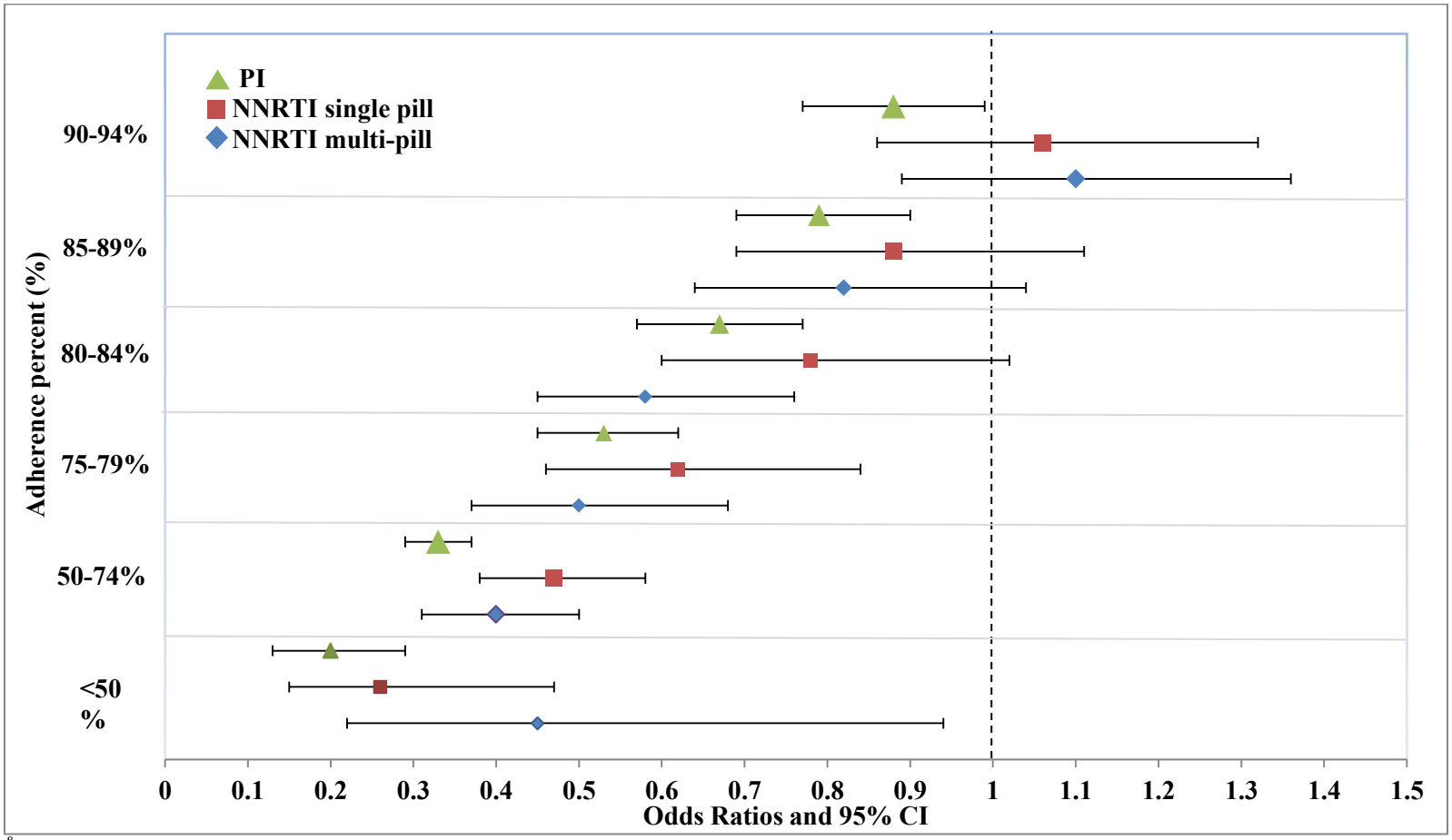
Figure 3.4. Proportion suppressed by adherence category (2006-2010)

N Person-years: 48,308



*Based on most dominant regimen used in the year;** INSTI-based regimen (2008-2010)

Figure 3.5. Odds ratios and 95% CI of HIV RNA suppression by adherence category (2006-2010)



[&]Adjusted for age, race alcohol abuse, major depression, drug abuse, geographical location, time since first HAART initiation

Appendix Table 3.1. Change in adherence over time (2001-2010)

N-person-years=82,217

Model	Time	Unadjusted estimate	Adjusted estimate
Model 1:	Per 1- year interval	0.07 (0.04, 0.10)	0.08 (0.04, 0.12)
Model 2:	Per 2- year interval	0.09 (0.03, 0.15)	0.13 (0.05, 0.20)
Model 3:	2006-11 vs. 2001-05	0.18 (0.001, 0.36)	0.16 (-0.04, 0.36)

[&]Adjusted for age, race, alcohol abuse, major depression, drug abuse, time since HAART initiation

Appendix Table 3.2. HIV RNA suppression by adherence category (odds ratios and 95% CI)

N person-years=46,291[*]

Adherence (%)	Unadjusted estimate	PS-weighted estimate[δ]
<50	0.26 (0.20, 0.34)	0.39 (0.26, 0.58)
50-74	0.36 (0.33, 0.39)	0.45 (0.39, 0.52)
75-79	0.51 (0.45, 0.58)	0.55 (0.46, 0.67)
80-84	0.66 (0.59, 0.74)	0.69 (0.58, 0.82)
85-89	0.77 (0.70, 0.85)	0.79 (0.67, 0.92)
90-94	0.94 (0.86, 1.03)	1.05 (0.91, 1.21)

*Excluding those with only one person-year; [δ]Average treatment effect using propensity score included as covariate in model: PS: P(receiving an NNRTI-based regimen=1)| age, race, geographical location, time since first HAART initiation, lagged CD4, lagged HIV RNA, lagged drug abuse, lagged alcohol abuse, lagged major depression), interaction between type of HAART and adherence

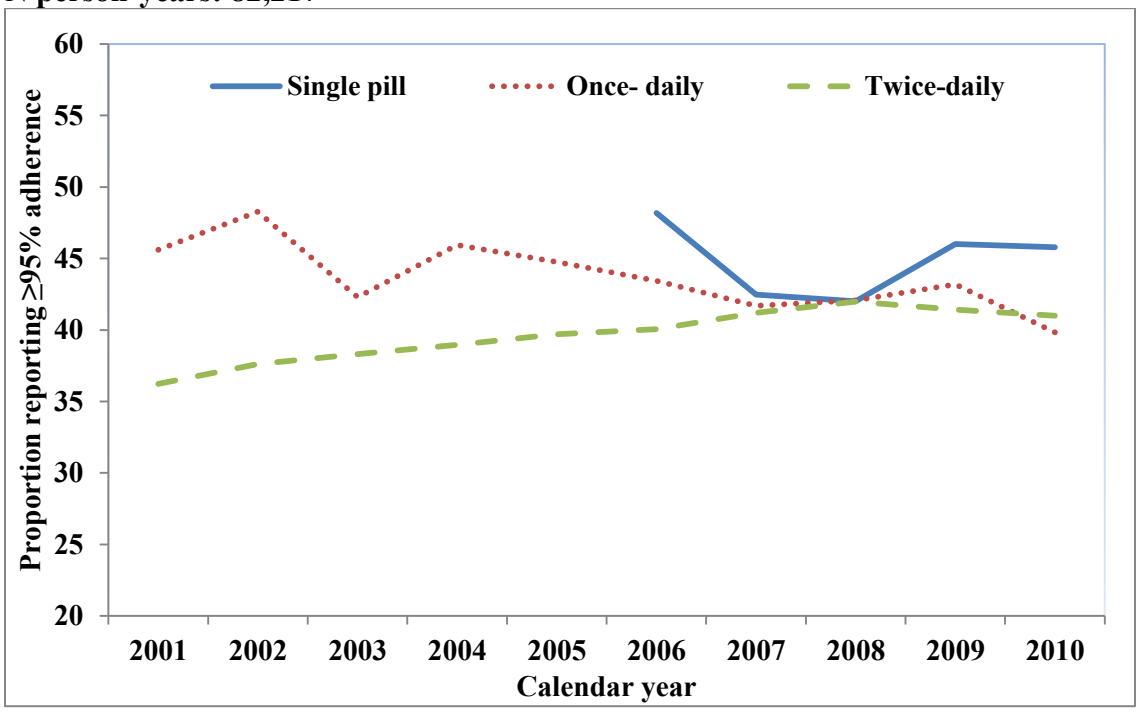
Appendix Table 3.3. HIV RNA suppression by adherence category (odds ratios and 95% CI)*

Adherence (%)	PS-weighted estimate First HAART N person-years: 6,937[#]	PS-weighted estimate ≥270 days N person-years:34,572[#]	PS-weighted estimate ≥330 days N person-years:21,756[#]
<75	0.58 (0.46, 0.73)	0.44 (0.36, 0.54)	0.49 (0.31, 0.76)
75-79	0.72 (0.51, 1.01)	0.62 (0.52, 0.74)	0.65 (0.42, 1.03)
80-84	1.02 (0.76, 1.37)	0.77 (0.67, 0.88)	0.95 (0.70, 1.30)
85-89	0.96 (0.74, 1.25)	0.87 (0.78, 0.98)	1.02 (0.83, 1.24)
90-94	1.18 (0.93, 1.49)	0.95 (0.86, 1.06)	1.04 (0.91, 1.19)

[*]Excluding those with only one person-year; [#]Average treatment effect using propensity score included as covariate in model; PS: P(receiving an NNRTI-based regimen=1)| age, race, geographical location, lagged CD4, lagged HIV RNA, lagged drug abuse, lagged alcohol abuse, lagged major depression)

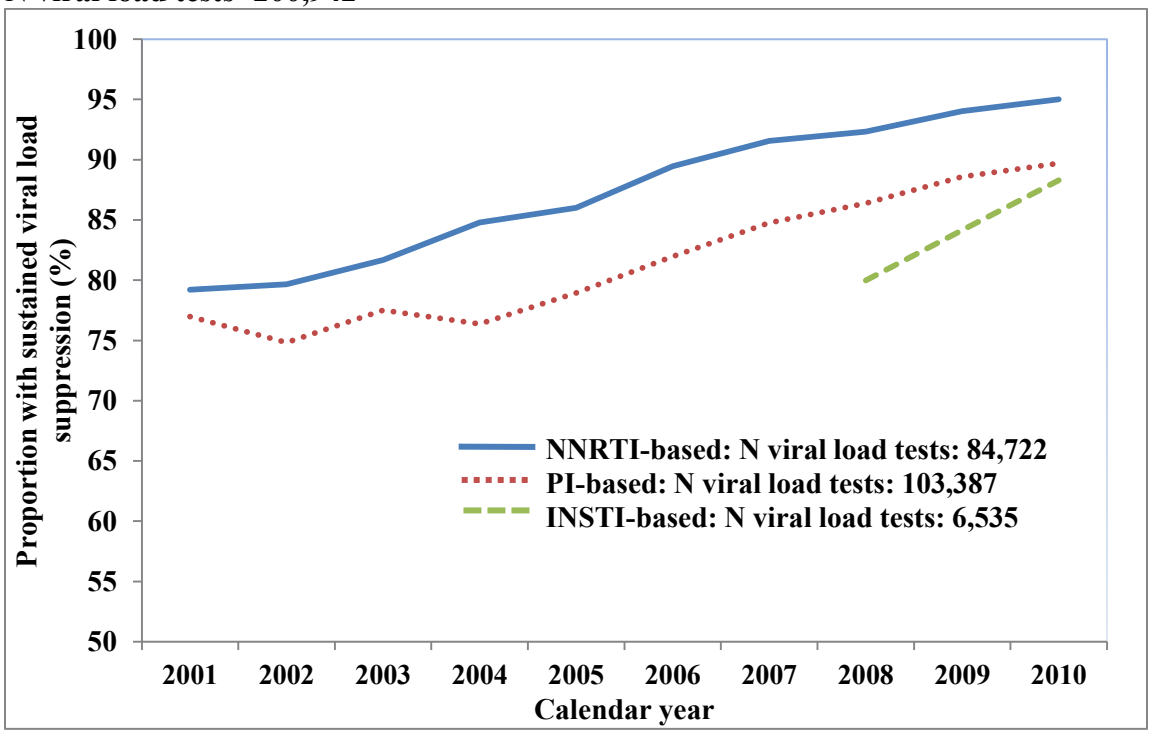
Appendix Figure 3.1 Distribution of ≥95% adherence by regimen type and daily dosing

N person-years: 82,217



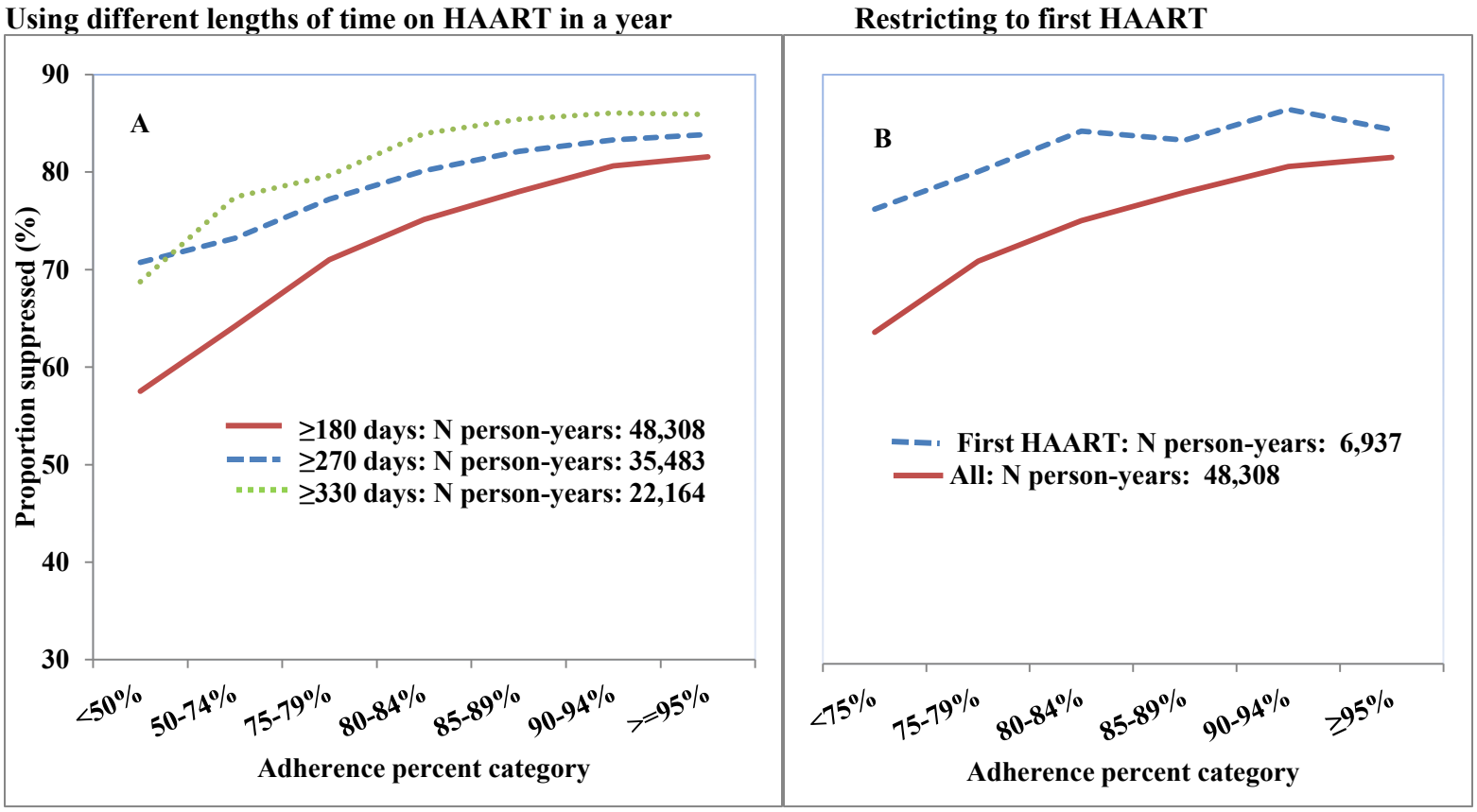
Appendix Figure 3.2. Proportion of person-years with sustained viral load suppression (2001-2010)*

N viral load tests=200,942



*Among persons with more than one viral load test in a year and persons with the first viral load test suppressed

Appendix Figure 3.3. Sensitivity analysis: suppression according to adherence



CHAPTER FOUR

The Effect of Concomitant Medication Use on Adherence to Highly Active Antiretroviral Therapy (HAART) in the Current Era of HIV Treatment

Abstract

Background

The introduction of highly active antiretroviral therapy (HAART) over the past decade has led a decrease in AIDS-related morbidity and mortality, and an increase in the prevalence of chronic non-AIDS comorbidities and their subsequent treatment. We sought to determine the effect of pill burden due to use of concomitant medications for non-AIDS comorbidities in HIV-infected persons on adherence to HAART.

Methods

We used longitudinal data from two prospective cohort studies – the Multicenter AIDS Cohort Study (MACS) and the Veterans Aging Cohort Study virtual cohort (VACS VC) between March 2001 and December 2011, and October 2000 and September 2010 respectively. In the MACS, adherence and the number of medications used for a chronic non-AIDS condition were calculated using self-reported measures (adherence over the previous 4 days and concomitant medication use since the prior visit). In the VACS, adherence and the total mean number of concomitant medications used for at least 90 days in a given year were calculated using pharmacy refill records. Random-effects logistic regression models were used to determine the effect of the number of concomitant medications used on the minimum optimal adherence to HAART, and propensity score weighting was used to adjust for using more than the mean number of concomitant medications.

Results

A total of 1,194 MACS participants contributed 11,678 person-years between 2001 and 2011, and 21,708 VACS patients contributed 79,972 person-years between 2001 and

2010. The number of concomitant medications used, and the proportion achieving minimum optimal adherence increased between 2006 and 2011, and this proportion was higher among persons older than 50 years, and persons with a higher VACS Risk Score. In the MACS, the odds of achieving minimum optimal adherence increased with an increase in the number of concomitant medications (≥4 vs. <2: 1.19 (0.75, 1.88)). In the VACS, the odds of achieving minimum optimal adherence increased with an increase in the number of concomitant medications for both NNRTI-based regimens (≥6 vs. <2: 1.84 (1.57, 2.15)), and PI-based regimens (≥6 vs. <2: 1.97 (1.75, 2.23)).

Conclusions

Even though the use of concomitant medications for chronic non-AIDS comorbidities led to improved adherence, comprehensive treatment management, regular monitoring of medication use, and counseling of persons with complex treatment regimens are necessary to sustain favorable treatment outcomes over long periods of time.

Background

In the past decade, there has been a steep increase in the life expectancy of HIV-infected persons which is now approaching that of uninfected persons.[1,2] Owing to prolonged survival, inflammation associated with HIV, and toxicities associated with highly active antiretroviral therapy (HAART), HIV-infected persons now have a higher burden of comorbidities.[3] The prevalence of non-AIDS comorbidities and the resultant use of medications co-administered with HAART have led to more complex treatment management in HIV-infected persons.

Early in the HAART era, increased antiretroviral (ARV) regimen complexity and pill burden were some of main barriers to achieving optimal adherence to HAART.[4,5] Nevertheless, newer and second-generation formulations have enabled the overcoming of the barriers as they are easier to administer, e.g., single pill combination of Efavirenz/Tenofovir/Emtricitabine (EFV/TDF/FTC) and drugs such as Ritonavir-boosted Atazanivir (ATV/r), Elvitegravir (ETV), and Raltegravir (RTG) have improved pharmacokinetic and toxicity profiles. As a consequence, adherence to HAART has become easier, and they do not necessitate high levels of adherence for viral load suppression.

The benefits of simplified, more safe and effective HAART regimens may however be complicated due to polypharmacy in HIV-infected persons.[6] Polypharmacy, defined as the use of five or more medications,[7] requires good access to care, including more health care visits, and also poses an increased risk for drug-drug interactions. Age is a strong predictor of polypharmacy,[8] and older HIV-infected persons use more

concomitant medications compared to younger HIV-infected persons.[9] The treatment of HIV and non-AIDS comorbidities is further complicated by the pathophysiology of aging in HIV-infected persons and illnesses such as chronic kidney disease and diabetes, which result in slow pharmacologic clearance and inconsistent drug absorption, eventually lowering drug effectiveness, and raising the risk for toxicity.[10] In addition to the use of concomitant medications, the treatment of several chronic non-AIDS comorbidities such as diabetes and hypertension requires additional time-intensive self-care activities like exercise and shopping for healthy food, which may further impact adherence to medications.[15]

However, older adults with HIV have better virological outcomes[10,11,12] owing to better retention in care and adherence to HAART.[13] Further, older persons are less likely to engage in risky behaviors that negatively impact adherence in persons with HIV and non-AIDS comorbidities such as substance abuse.[14,15] For all persons on concomitant medications, improvement in the overall symptoms from comorbidities may further serve as a motivator for maintaining high levels of adherence to treatment over time.[14,16]

There is a need to determine if improvement in HAART formulations is counterbalanced by increased treatment complexity due to concomitant non-AIDS medication use which is increasing in aging HIV-infected persons. We sought to determine the impact of using concomitant medications on adherence to HAART in a population of treated HIV-infected persons using data from two long-standing cohort studies.

Methods

We used longitudinal data collected prospectively from participants in the Multicenter AIDS Cohort Study (MACS), and pharmacy fill/refill data, laboratory and clinical data from the Veteran Aging Cohort Study virtual cohort (VACS VC).

Source populations

The MACS is an ongoing prospective study of the natural history of HIV-1 infection in men who have sex with men (MSM) in the United States.[17] Eligible persons had to be sexually active, 18 years or older, and free an AIDS-defining illness, i.e., opportunistic infection or malignancy.[18] Every six months, participants came to study visits which consisted of physical examinations, collection of blood for concomitant laboratory testing and storage, and collection of information on medical history, prescription medication use, demographics, and behaviors through standardized interviews. MACS study protocols were approved by institutional review boards at each study center, and informed consent was obtained from all participants.

The VACS VC is a large ongoing, prospective clinical cohort of HIV-infected persons in care at Veterans Health Administration (VHA) centers nationwide.[19] Details of the VACS VC have been previously described.[19] We obtained laboratory and clinical data, and outpatient prescriptions for each patient by linking Immunology Case Registry, and Pharmacy Benefits Management (PBM) Registry records, respectively.[20]

Definition of HAART

HAART was defined using the DHHS guidelines as 'a combination ARV treatment regimen containing at least 3 ARV drugs - 2 nucleoside reverse-transcriptase inhibitor (NRTI) medications plus a protease inhibitor (PI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (INSTI)'.[21] In the MACS, the date of HAART initiation was set as the visit date of the first HAART report. In the VACS, the year of HAART initiation was set as the year of first HAART report. For each person-year, we used the regimen most frequently refilled to classify HAART as NNRTI-based, PI-based (including users of PIs, and both NNRTIs and PIs), INSTI-based, or 3 NRTI containing abacavir or tenofovir.

Study population

For this analysis, the MACS was restricted to HIV-positive men who reported HAART use at any time from March 1, 2001 to December 31, 2011. Only visits at which participants reported using HAART were included in the analysis. In the VACS, only person-years in which HAART was used for at least 180 days in the year were included. The analysis used longitudinal pharmacy refill data collected prospectively from HIV-positive persons on HAART and followed in the VACS from October 1, 2000 through September 30, 2010.

Outcomes and Exposures

Adherence to HAART was defined using self-reported information collected at the study visits in the MACS. The participant was asked about his actual use of each ARV medication over the four days prior to the study visit. These responses were compared to the prescribed usage to determine adherence;

$$\frac{\text{Sum of the number of times the patient took the drug over a 4-day period} * 100}{\text{Sum of the number of times they were expected to take the drug each day} * 4}$$

Adherence to HAART was treated as a continuous variable, or dichotomized as ≥85% or less, which had been established as the minimum optimal adherence in the current era of treatment in the MACS.[22]

In the VACS, we calculated adherence to HAART using the medication possession ratio defined by Steiner and colleagues[23] which measures the duration of time the patient had the medications available, relative to the total number of days between refills. This was calculated for each person-year that contained at least one refill as follows:

$$\frac{\sum_{ARVs} Number\ of\ days\ supplied\ with\ drug\ in\ a\ year}{\sum_{ARVs} Total\ number\ of\ days\ between\ first\ and\ last\ refill} * 100$$

We excluded stockpilers (20.2% of study population), defined as person-years with a refill frequency exceeding the scheduled dosing interval by more than 5% since the Steiner algorithm was not validated in this subgroup.[20,24] Adherence to HAART was treated as a continuous variable or dichotomized as ≥85% for person-years on NNRTI-based regimens, and ≥95% for person-years on INSTI-based and PI-based regimens

respectively, which were established as minimum optimal adherence cutoffs by HAART regimen type (Chapter 3).

Concomitant medication use in the MACS was calculated based on self-reported use of non-AIDS medications since the prior MACS visit. We classified drugs into pharmacological classes using the WHO Anatomical Therapeutic Chemical Classification (ATC) system,[25] and further classified them into chronic use medications and short-term use medications. Our primary exposure variable was the number of medications used for chronic non-AIDS conditions. Appendix 4.1 lists the pharmacological classes used in our study populations.

Concomitant medication use in the VACS was defined as the use of medications for non-AIDS conditions on a long-term basis.[26,27] We determined receipt of all outpatient non-AIDS formulations dispensed through the VHA using pharmacy fill/refill data available through the PBM program.[19] We defined concomitant medication use as using medications for at least 90 days in a year with a 30-day gap for fill-refill.[26] Medications were classified into pharmacological classes using the Department of Veterans Affairs (VA) drug classification system.[28] We excluded pharmacy fill/refills classified as diagnostic supplies, emollients, eye washes and lubricants, soaps, shampoos and soap-free cleaners, mouthwashes, sun protectants and screens, irrigation solutions, ceruminolytics, deodorants and antiperspirants, and contact lens solutions from our analyses.[26] We determined the total mean number of non-ARV long-term medications received for each patient during each year in the study time period as follows:[26]

$$\frac{\sum_{non-ARVs}(Medication\ refilled) * (Number\ of\ days\ in\ refill)}{Number\ of\ days\ in\ the\ year\ when\ at\ least\ one\ medication\ for\ a\ non\text{-}AIDS\ condition\ was\ used}$$

Appendix 4.3 shows an example describing the calculation of the total mean number of non-ARV long-term medications received for each patient.

In the MACS, potential predictors of adherence and concomitant medication use were sociodemographic and behavioral characteristics reported for the 6 months prior to when adherence and concomitant medication use were ascertained. These included age, race, annual income (<$10,000 versus ≥$10,000), insurance status (private, public, none), current injection drug use, non-injection drug use (including cocaine, crystal methamphetamine, marijuana, heroin, poppers), current smoking, and moderate-heavy alcohol intake (3-4 drinks/day for more than once a month) compared to lower quantities. Treatment and disease characteristics included CD4 cell count (quantified using standardized flow cytometry)[17] and HIV RNA levels (determined using the Roche Ultrasensitive RNA PCR assay (Hoffman-LaRoche, Nutley, NJ, U.S.A.) with a detection limit of 50 copies/ml),[17] lagged to the previous visit, and number of ARV medications, history of AIDS (confirmed by medical record review) and non-AIDS comorbidities at each visit. The presence of diabetes, hypertension, dyslipidemia, liver disease, and kidney disease were determined using algorithms based on a combination of self-reported diagnosis and treatment, or based on clinical indices including laboratory test results for at least two consecutive visits. Depression was defined if treatment was self-reported or depressive symptoms were present as indicated by a Centers for Epidemiologic Studies

Depression Scale (CES-D) score greater than 16.[29] Other chronic non-AIDS comorbidities were defined using ICD-9 diagnosis codes on medical records obtained to confirm self-reported information. We also controlled for the type of HAART regimen (NNRTI-based, PI-based, INSTI-based, and single pill), and the short-term use of non-ARV medications (only if participants reported using them over the past 4 days).

In the VACS, potential confounders of HAART adherence and concomitant medication use included sociodemographic, behavioral, disease and treatment characteristics. Fixed characteristics included race, smoking, and geographical location obtained at the first time seen after October 1, 2000 (baseline). Time-varying factors included the number of ARV medications used, and the HAART regimen type. Non-AIDS comorbidities, AIDS status, and behaviors such as alcohol abuse and drug abuse were defined by ICD-9 diagnostic codes, and they required at least one inpatient or two outpatient diagnoses in a given year.[30,31] We also adjusted for the VACS Index, which is a composite score of prognostic markers in treated HIV patients. This includes age, CD4 cell count, HIV RNA and laboratory measurements of hemoglobin, aspartate and alanine transaminase (AST, ALT), platelets, creatinine, HCV status and composite markers of liver and renal injury.[32]

Statistical Methods

We restricted the analysis to person-visits with non-missing covariates, representing about 95% of the sample. We graphically depicted temporal trends of

concomitant medication use from 2001-2011, and compared the concomitant medication use by adherence levels, age (<50 years vs. ≥ 50 years), and HAART regimen type.

To examine the effects of concomitant medication use on adherence, we restricted the time to 2006 and onwards. We obtained adjusted probabilities for achieving the minimum optimal adherence using random-effects logistic regression models. In the MACS, using random-effects logistic regression models with minimum optimal adherence as a dichotomous outcome (≥85% and <85%), we examined the association between HAART adherence and the number of concomitant medications as a categorical variable (<2, 2-3, ≥4). Since characteristics informing prescribing patterns may affect adherence and the number of concomitant medications, we adjusted for possible confounding by indication using propensity scores to weight the model. The propensity score for using greater than the mean number of concomitant medications for a non-AIDS condition was determined by logistic regression which included age, race, insurance status, alcohol use, smoking, non-injection drug use, injection drug use, depression, type of HAART, calendar year, viral load suppression and adherence lagged to previous visit. Weights were generated as the average treatment effect for the treated (ATT), trimmed at the 95th percentile, and included in the repeated measures logistic regression model as a covariate. In the VACS, using random-effects logistic regression models adjusted for confounders, we examined the association between minimum optimal adherence and the number of concomitant medications (<2, 2-3, 4-5, ≥6) using separate models for HAART regimen type, since the minimum optimal adherence differed by regimen type in the population. We did not use propensity scores for

adjustment of confounders in the VACS since we had sufficient power to directly adjust for confounders in the primary regression model.

Using multinomial logistic regression with HAART regimen type as a categorical outcome variable, we determined the effect of the number of concomitant medications on HAART regimen type, adjusted for confounders. In order to examine the relationship between adherence and the number of concomitant medications used by the pharmacologic class of the concomitant medication, persons were classified as using medications from a particular pharmacologic class if they used at least one long-term medication from that class each year. In the MACS, the most frequently used classes of medications were determined, and we examined the association between adherence and the number of concomitant medications separately for each of these classes, both cross-sectionally at the incident visit (defined as the first visit at which they reported using a drug from a given medication class), and longitudinally at visits following the incident visit. In the VACS, we used the same pharmacologic classes used in the MACS, since they represented some of the most commonly used medication classes in the literature.[9] To examine the association between concomitant medication use and HAART adherence at the incident visit in the cross-sectional dataset, we used a linear regression model with HAART adherence as a continuous outcome and the number of concomitant medications as a continuous exposure variable, adjusted for confounders. We examined the association between the minimum optimal HAART adherence and the number of concomitant medications using a random-effects logistic regression model among those using the drug in more than one year during follow-up.

All analyses were performed using SAS 9.2 (Cary, North Carolina, USA) and STATA 12.1 (College Station, Texas, USA). A p-value threshold of 0.05 was used to define statistical significance.

Results

A total of 1,194 MACS participants contributed 11,678 person-years between 2001 and 2011, and 21,708 VACS patients contributed 79,972 person-years between 2001 and 2010. Characteristics of the MACS study population are shown in Table 4.1A and characteristics of the VACS study population are shown in Table 4.1B according to concomitant medication use.

Unadjusted, in the MACS, using more than one concomitant medication (mean number of concomitant medications=2) was associated with older age, not being black, having higher incomes, smoking, but not using alcohol and recreational drugs. A majority of the persons using multiple concomitant medications had a higher CD4 cell count and a significantly higher proportion were virally suppressed compared to persons using less than 2 medications. Most persons used either a PI-based or NNRTI-based regimen, but the proportion using an INSTI-based regimen was significantly higher among those using multiple medications (9.0% vs. 2.6%, $P<0.001$).

In the VACS, at baseline, the mean age was 45.7 years (standard deviation (SD): 9.9), 98% were male, 46.6% were black, 57.2% were smokers, and almost 47% lived in the south. Unadjusted, the use of multiple concomitant medications was associated with older age, and higher rates of alcohol abuse, drug abuse and depression. Persons using

more medications had a higher mean VACS Index, and used more PI-based and INSTI-based regimens compared to those using less than the mean number of medications (mean=4).

Concomitant medication use

Figures 4.1 and 4.2 show the number of concomitant medications used by calendar time (Figure 4.1), and adherence level (Figure 4.2). In the MACS, the number of concomitant medications used increased slowly over time, with an increase in the upper quartile of the distribution between 2001 and 2005 (Figure 4.1A). As shown in Figure 4.2A, persons with adherence greater than 85% used more concomitant medications compared to persons with adherence lower than 85% (Median (IQR): 1 (3) vs. 1 (2)). Similar to the MACS, the number of concomitant medications used increased slowly over time in the VACS (Figure 4.1B), and, it increased at higher levels of adherence as well (Figure 4.2B). Based on results from the logistic regression model used to obtain the propensity score in the MACS, significant predictors of using more than the mean number of concomitant medications in the current era of treatment were older age, white race, having insurance coverage, smoking, non-injection drug use, depression, using an INSTI-based regimen, and increasing levels of adherence and viral load suppression.

In the VACS, using NNRTI-based regimens was associated with a lower number of concomitant medications compared to PI-based and INSTI-based regimen users (Appendix Figure 4.1). Figures 4.3A and 4.3B show results from the multinomial regression model looking at the relationship between HAART regimen type and number

of concomitant medications. In the MACS, persons with more than 4 medications were 1.5 times more likely to be on an INSTI-based regimen compared to an NNRTI-based regimen, and 83% less likely to be on a PI-based regimen compared to an NNRTI-based regimen. In the VACS, persons with more than 6 medications were 2.3 times more likely to be on an INSTI-based regimen compared to an NNRTI-based regimen, and almost as likely to be on a PI-based regimen compared to an NNRTI-based regimen (RR: 1.06).

Class of concomitant medications

Figures 4.4A and 4.4B show the type of concomitant medications used most frequently. In the MACS, lipid modifying agents (24.5%), CNS stimulants (15.5%), agents acting on the renin-angiotensin system (ACE inhibitors), (7.4%), drugs used in diabetes (5.9%) and beta-blockers (5.3%) were among the most frequently used classes between 2006 and 2011. In the VACS, lipid modifying agents (5.3%), antidepressants (5.2%), ACE inhibitors (3.7%), antirheumatic agents (3.4%) and non-opioid analgesics (3.2%) were the five most frequently used classes between 2006 and 2010. Further, in the MACS, the use of different classes of concomitant medications did not change over time, but they differed among age groups (Appendix Figure 4.3). Compared to persons younger than 50 years, older persons had a higher proportion using medications for cardiovascular disorders and diabetes, and a lower proportion using CNS stimulants over time.

Relationship between concomitant medication use and adherence

In both cohorts, the proportion achieving minimum optimal adherence increased with the number of concomitant medications, and was higher among persons older than 50 years (Figures 4.5A and 4.5B), and persons with a higher VACS Index (Appendix Figure 4.2). This trend was consistent across all regimen types, although the proportion achieving minimum optimal adherence was higher among NNRTI-based regimen users.

The adjusted probability of achieving minimum optimal adherence increased with use of more concomitant medications in the MACS (Figure 4.6A). The probability of achieving minimum optimal adherence was significantly higher among those using more than 3 concomitant medications compared to those using less than 2 concomitant medications (0.97 (0.96, 0.98) vs. 0.95 (0.94, 0.96)), respectively. Random-effects logistic regression models weighted for the propensity score and adjusted for non-AIDS medications used for an acute condition taken in the past 4 days showed that the odds of achieving the minimum optimal adherence increased with an increase in the number of concomitant medications (≥2 vs. <2: 1.28 (0.95, 1.73)). The adjusted odds of achieving the minimum optimal adherence were attenuated compared to the unadjusted odds for the covariates of interest: age ≥50 (1.22(0.69, 1.73), race (white vs black: 1.54 (1.08, 2.20)), alcohol use (Yes vs. No (0.84 (0.62, 1.12)), smoking (Yes vs. No (0.91 (0.68, 1.22)) and depression (Yes vs. No (0.87 (0.64, 1.17)) (Table 4.2A).

In the VACS, the adjusted probability of achieving minimum optimal adherence increased with an increase in the number of concomitant medications for all HAART regimen types (Figure 4.6B). The probability of achieving minimum optimal adherence

was significantly higher for users of NNRTI-based regimens compared to those using PI-based regimens and INSTI-based regimens. Longitudinally, the odds of achieving minimum optimal adherence increased with an increase in the number of concomitant medications for both NNRTI-based regimens (≥6 vs. <2: 1.84 (1.57, 2.15)), and PI-based regimens (≥6 vs. <2: 1.97 (1.75, 2.23)) (Table 4.2B). The adjusted odds of achieving the minimum optimal adherence were almost unchanged compared to the unadjusted odds for the covariates of interest for both NNRTI-based and PI-based regimens.

Figures 4.7A and 4.7B show the change in adherence after the use of a concomitant medication between 2001 and 2011. In both cohorts, there was an increase in adherence following the start of the medication if the baseline adherence was lower than 50%. At higher levels of baseline adherence, there was a decrease in adherence following the use of a concomitant medication.

Incident use of concomitant medications from a particular class

Figures 4.8A and 4.8B show results from five linear regression models with adherence percent as a continuous outcome, and concomitant medication use as a continuous exposure variable based on the use of at least one drug from each of the five pharmacologic classes. At the incident visit in the MACS, there was a decrease in adherence with an increase in the number of concomitant medications for persons using at least one 'lipid modifying agent', 'drug used in diabetes', 'CNS stimulants', or 'beta-blockers', but there was a 1% increase in adherence with the use of every concomitant medication among persons using at least one ACE inhibitor (Figure 4.8A). None of these

estimates were statistically significant. We examined similar classes in the VACS, but due to the higher prevalence, studied antidepressants instead of CNS Stimulants. There was a slight increase (<1%) in adherence with an increase in the number of concomitant medications for persons at the incident visit for each of the five medication classes, and the estimates were statistically significant (Figure 4.8B).

Longitudinal use of concomitant medications from a particular class

Figure 4.9A shows results from five distinct repeated measures logistic regression models with minimum optimal adherence as a dichotomous outcome and concomitant medication use as a dichotomous exposure variable (≥mean number of medications vs. <mean number of medications) based on the use of at least one drug from each of the five pharmacologic classes in the MACS. The odds of achieving minimum optimal adherence was higher among those using more than the mean number of concomitant medications compared to those using less than the mean number of concomitant medications for persons using at least one drug from the pharmacological classes: 'lipid modifying agents', 'ACE inhibitors', and 'drugs used in diabetes' but the results were not statistically significant.

Figure 4.9B shows results from five distinct repeated measures logistic regression models with minimum optimal adherence as a dichotomous outcome and concomitant medication use as a dichotomous exposure variable (≥mean number of medications vs. <mean number of medications) based on the use of at least one drug from each of the five pharmacologic classes in the VACS. Over time, the odds of achieving minimum optimal

adherence was higher among those using more than the mean number of concomitant medications compared to those using less than the mean number of concomitant medications for persons using at least one drug from pharmacological classes: 'antilipemics', 'ACE inhibitors', 'beta-blockers', 'antidepressants' and 'oral hypoglycemics' after accounting for within-person changes and adjusting for confounders.

Discussion

Polypharmacy and treatment complexity have been shown to impact adherence to HAART in HIV-infected persons.[4,5] In our study populations of aging and treatment-experienced HIV-infected MSM and veterans, the use of concomitant medications for chronic non-AIDS comorbidities has increased since 2001, in parallel with a rising burden of comorbidities.[7] As observed in prior studies using these populations, adherence has improved over time, and the proportion achieving minimum optimal adherence has increased over time. Longitudinally, the adherence to HAART was positively impacted with an increase in the number of concomitant medications used.

Independent predictors of minimum optimal adherence to HAART in both cohorts such as lower prevalence of alcohol use, smoking, and depression, are consistent with behaviors associated with optimal adherence in other studies.[33,34] Similar to previous studies in HIV-infected populations and the general population, [9,10,32] variables associated with the prevalence of comorbidities such as age and VACS Index were strongly associated with concomitant medication use in our study populations. In both cohorts,

older individuals used more concomitant medications, and were more likely to achieve minimum optimal adherence compared to younger individuals. This finding was consistent with a recent meta-analysis on aging and adherence to HAART which showed that the aging population had better adherence to treatment, as they "may be more organized and experienced in their daily lives, or possibly more motivated after experiencing the initial devastating outcomes of the AIDS epidemic".[13] In contrast, persons with a lower VACS Index (i.e., younger and lower risk for morbidity and mortality),[32] had a slightly higher proportion achieving minimum optimal adherence when adjusted for the number of concomitant medications. This could be attributed however to viral load suppression (an integral component of minimum optimal adherence and the VACS Index), which is associated with both a higher minimum optimal adherence and a lower VACS Index.

Provider decisions regarding the type of ARV or non-ARV medication used may be largely influenced by the potential for pharmacologic drug-drug interactions between ARV and non-ARV medications.[35] The DHHS guidelines suggest regimen modification and dosing changes to prevent drug-drug interactions as a result of polypharmacy.[21] Both NNRTI- and PI-based regimens are substrates and either inducers or inhibitors of cytochrome P-450 (CYP450),[21,36] an enzyme which is responsible for the majority (approximately 75%) of all drug metabolism.[37] INSTI-based regimens do not impact CYP450 enzymes, and compared to other HAART regimens, they have an improved safety profile and fewer drug-drug interactions as a result of which, they are more likely to be used in patients with complex regimens. A recent study found that compared to

INSTI-based regimens, PI-based regimens and NNRTI-based regimens had a significantly higher prevalence of drug-drug interactions (PI: prevalence ratio (PR): 4.96; NNRTI: PR: 2.48).[21,36] Our finding that use of more concomitant medications was associated with the use of INSTI-based regimens compared to NNRTI-based regimens, is therefore consistent with recommended treatment guidelines and results from previous studies.[21] In addition to safety and effectiveness considerations, PI-based regimens have a higher pill burden than other regimen types, and this could explain in part the preference of NNRTI-based regimens compared to PI-based regimens in persons using more concomitant medications in the MACS.

The profile of concomitant medications used in these cohorts is similar to that reported in other HIV populations.[8,35] In both cohorts, lipid modifying agents were the most commonly used class of medications, followed by ACE inhibitors, beta-blockers, and oral hypoglycemics. In the VACS, there was a high prevalence of antirheumatic agents and opioid analgesic use. This is comparable to the general veteran population, which has a 43% higher prevalence of chronic pain conditions compared to other American adults, and majority of the veteran population receives prescriptions for one or more analgesics.[38,39] HIV-infected veterans in the VACS also had a higher prevalence of use of antidepressants compared to the MSM population in the MACS.

The use of more concomitant medications was associated with significantly higher odds of achieving minimum optimal adherence in both cohorts. Furthermore, we found that in the current era of treatment, 84.2% and 77.0% were suppressed in the MACS and the VACS respectively, consistent with that reported for other HIV-infected

populations (75-80%).[40,41] Our finding of high adherence to HAART and sustained suppression despite high overall pill burden could be attributed to a better understanding of the effects of missed doses of HAART, and "linking disease symptoms to not taking medications".[15] In a recent study by Monroe et al, one of the emerging themes in the focus group discussions was the link between a good understanding of the health conditions and treatment adherence.[15] Experiencing physical manifestations of their illnesses and the fear of high morbidity and mortality may have therefore acted as a motivator for better adherence to prescribed treatments for HIV.

Albeit limited and conflicting, research findings also suggests that persons managing HIV and non-AIDS comorbidities tend to prioritize adherence to HAART over adherence to non-ARVs due to perceptions regarding the relative severity of HIV as an illness.[15,16] Although we did not investigate adherence to concomitant medications in our study, this has been shown previously to be a predictor of adherence to HAART.[42] Our restriction to the use of at least one medication from a given pharmacologic class was to determine if our finding of improved adherence with more concomitant medications varied by the type of concomitant medication used. The class of concomitant medication prescribed is innately linked to the comorbidity, the type of HAART regimen prescribed, and other patient characteristics such as age, substance use, other conditions, and results from clinical indices. Given that our findings were unchanged even after this restriction, we can conclude that the class of concomitant medication did not influence the association between adherence to HAART and number of concomitant medications for chronic non-AIDS conditions.

There were several limitations in our study. The use of concomitant medications was self-reported in the MACS, which may be associated with recall error. We were not able to further ascertain if the medications were taken as prescribed in the VACS. When examining the adjusted relationship between minimum optimal adherence and the number of concomitant medications, we observed an attenuation of the estimates in the MACS but only slight changes to our estimates in the VACS. This may be due to unaccounted bias arising from substance use (i.e., smoking, injection drug use, non-injection drug use). There are significant differences in the prevalence of non-AIDS comorbidities in male and female HIV-infected persons.[43,44] Given that our cohorts are largely male-dominated, the generalizability of our findings to women may therefore be limited. Another limitation may be the overrepresentation of persons with good access to care since the VACS population was insured through the VA PBM program,[45] and in the MACS, a high proportion (93%) reported being insured. Further, as hypothesized by other studies, there may be potential selection bias due to the use of an older, treatment-experienced population, with good access to care.[13]

Our study had strengths as well. We used data from two long-standing observational cohort studies of HIV-infected persons in the United States, with a mean of 7 years on HAART at the end of 2010, a mean age greater than 45 years, and using on average, more than 2 concomitant medications for a chronic non-AIDS condition. Although the MACS and the VACS consist of markedly different HIV-infected populations and use different measures of our primary exposure and outcome variables, it was interesting to note that our findings related to adherence to HAART and concomitant

medication use were similar using both cohorts. We were able to determine that the improvement in HAART formulations was not counterbalanced by increased treatment complexity due to concomitant medication use for chronic non-AIDS comorbidities, and this finding will lead to a better understanding of the current treatment scenario.

Conclusions

Notwithstanding the positive impact on adherence to HAART by increased non-ARV pill burden, there is a need to invest resources into the management of non-AIDS comorbidities. Comprehensive counseling and medication therapy management must be provided for patients with multiple comorbidities to improve overall adherence to medications, minimize potential drug-drug interactions, and optimize overall treatment outcomes.[9] While clinically significant drug-drug interactions and contraindications are well documented, continuous monitoring of the patients' medication use patterns is necessary, given the increasing burden of polypharmacy. In the light of increasing regimen complexity due to polypharmacy, future studies must attempt to tease apart associations between adherence to individual concomitant medications, and adherence to HAART, and focus their attention on low adherers.

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Table 4.1A. Study population characteristics in the MACS (2001-2011)

(N person-years=11,678, N=1,194)

	Concomitant medications<2 N person-years: 6,748, %	**Concomitant medications≥2 N person-years: 4,930, %**	**P-value**
Age, mean (SD)	46.4 (8.4)	52.7 (8.0)	<0.001
Black	30.3	19.7	<0.001
Alcohol use	15.1	11.8	<0.001
Smoking	38.6	46.9	<0.001
Injection drug use	1.8	1.8	1.0
Non-injection recreational drug use	50.1	45.5	<0.001
Insurance			
Public	56.7	55.3	0.17
Private	64.2	65.6	0.15
Other	7.0	5.0	<0.001
Income ≥$10,000	77.3	83.1	<0.001
Viral load suppression	75.4	82.2	<0.001
Non-AIDS Comorbidity (at least one)*	70.8	96.6	<0.001
AIDS status	13.3	19.6	<0.001
CD4 count	572.2 (278.0)	591.3 (281.0)	<0.05
HAART regimen			
NNRTI-based	45.1	41.2	<0.001
PI-based	46.1	46.7	0.52
INSTI-based	2.6	9.0	<0.001
3 NRTI	6.2	3.1	<0.001
Baseline visit after 2001	53.9	34.3	<0.001

*includes diagnosis of depression, diabetes, hypertension, dyslipidemia, liver disease, kidney disease, cardiovascular outcome, HBV, HCV, and other non-AIDS outcome

Table 4.1B. Study population characteristics in the VACS (2001-2010)

(N person-years=79,972, N=21,708)

Characteristics	**Baseline N persons=21,708**	**Concomitant medications<4 N person-years: 45,673**	**Concomitant medications>=4 N person-years: 34,299**
Age, mean (SD)	45.7 (9.8)	44.1 (9.7)	47.8 (9.0)
Black	46.6	45.2	43.6
Male	98.0	98.1	98.0
Smoking at baseline	57.2	-	-
Alcohol abuse $^{\delta}$	10.6	6.9	11.1
Drug abuse $^{\delta}$	13.5	9.2	14.3
Depression status$^{\delta}$	7.8	5.1	11.0
CD4 count (cells/mm^3), mean (SD)	422.5 (266.3)	512.2 (273.8)	471.1 (291.7)
Geographical location*			
Northeast	23.4	25.1	24.3
Midwest	13.8	13.1	13.4
South	46.5	46.4	44.7

Characteristics	Baseline N persons=21,708	Concomitant medications<4 N person-years: 45,673	Concomitant medications>=4 N person-years: 34,299
West	16.3	15.4	17.5
Viral load suppression	51.2	66.9	66.0
VACS Index (complete)	27.0 (20.4)	22.6 (17.6)	32.9 (20.9)
Non-AIDS comorbidity (at least one)	68.8	63.6	87.8
AIDS status			
	10.2	5.4	10.1
HAART regimen			
NNRTI-based	42.1	42.4	38.1
PI-based	52.8	51.9	54.6
INSTI-based	1.2	2.2	4.0
3 NRTI	3.9	3.5	3.3

*Northeast: CT, ME, MA, NH, NJ, NY, PA, MD, DC, DE, RI, VT; Midwest: IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; South: AL, AR, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV; West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; $^{\delta}$ Based on ICD-9 diagnosis codes

Table 4.2A. Crude and adjusted associations between minimum optimal adherence and number of concomitant medications use and covariates in the MACS (2006-2011)

	Unadjusted OR (95% CI) of adherence ≥85%	Adjusted OR (95% CI) of adherence ≥85%*
Number of concomitant medications		
2-3	1.47 (1.10, 1.97)	1.24 (0.91, 1.68)
≥4	1.68 (1.16, 2.44)	1.10 (0.69, 1.73)
Age ≥50 years (vs. <50 years)	1.72 (1.30, 2.29)	1.22 (0.69, 1.73)
Race^		
White	2.07 (1.44, 2.98)	1.54 (1.08, 2.20)
Other	0.80 (0.51, 1.27)	0.82 (0.53, 1.26)
Alcohol use (Yes vs. No)	0.75 (0.56, 1.01)	0.84 (0.62, 1.12)
Smoking (Yes vs. No)	0.68 (0.51, 0.93)	0.91 (0.68, 1.22)
Depression status (Yes vs. No)	0.74 (0.57, 0.97)	0.87 (0.64, 1.17)
Type of HAART[&]		
PI-based regimen	0.72 (0.53, 0.98)	0.76 (0.57, 1.01)
INSTI-based regimen	1.37 (0.81, 2.30)	1.28 (0.77, 2.15)

*Odds ratios come from a repeated measures logistic regression model adjusted for number of concomitant medications, age, race, insurance status, alcohol use, smoking, non-injection drug use, injection drug use, depression, type of HAART, viral load suppression and adherence lagged to previous visit, non-chronic non-AIDS medications taken in the past 5 days, calendar year; ^Reference group for race is black; [&]Reference group for type of HAART is NNRTI-based regimen

Table 4.2B. Crude and adjusted associations between minimum optimal adherence and number of concomitant medications and covariates by HAART regimen type in the VACS (2006-2010)

NNRTI-based regimen (N person-years: 19,931)

	Unadjusted OR (95% CI) of adherence ≥85%	**Adjusted OR (95% CI) of adherence ≥85%***
Number of concomitant medications		
2-3	0.97 (0.85, 1.10)	1.0 (0.89,1.14)
4-5	1.46 (1.25, 1.70)	1.50 (1.28, 1.75)
≥6	1.81 (1.56, 2.10)	1.84 (1.57, 2.15)
Age ≥50 years (vs. <50 years)	1.70 (1.50, 1.92)	1.46 (1.29, 1.67)
Race ^		
White	2.81 (2.48, 3.19)	2.38 (2.10, 2.70)
Other	1.73 (1.44, 2.07)	1.58 (1.32, 1.89)
Alcohol abuse (Yes vs. No)	0.55 (0.46, 0.65)	0.74 (0.61, 0.89)
Drug abuse (Yes vs. No)	0.46 (0.39, 0.54)	0.60 (0.51, 0.72)
Depression status (Yes vs. No)	0.88 (0.73, 1.06)	0.88 (0.72, 1.06)
VACS Risk Score greater than mean (vs. less than mean)	0.87 (0.79, 0.97)	0.76 (0.68, 0.85)

*Odds ratios come from a repeated measures logistic regression model adjusted for number of concomitant medications, age, race, alcohol abuse, drug abuse, major depression diagnosis, adherence and viral load suppression lagged to previous visit, calendar year, presence of a non-AIDS comorbidity, AIDS diagnosis, number of antiretrovirals; ^Reference group for race is black; reference group for number of concomitant medications:<2

PI-based regimens (N person-years: 23,647)

	Unadjusted OR (95% CI) of adherence ≥95%	Adjusted OR (95% CI) of adherence ≥95%*
Number of concomitant medications		
2-3	1.02 (0.92, 1.13)	1.08 (0.97, 1.20)
4-5	1.30 (1.15, 1.47)	1.37 (1.22, 1.55)
≥6	1.89 (1.68, 2.13)	1.97 (1.75, 2.23)
Age ≥50 years (vs. <50 years)	1.71 (1.55, 1.88)	1.59 (1.44, 1.76)
Race ^		
White	1.99 (1.81, 2.19)	1.76 (1.60, 1.94)
Other	1.52 (1.31, 1.75)	1.40 (1.21, 1.61)
Alcohol abuse (Yes vs. No)	0.68 (0.59, 0.77)	0.82 (0.70, 0.95)
Drug abuse (Yes vs. No)	0.68 (0.60, 0.76)	0.87 (0.76, 0.99)
Depression status (Yes vs. No)	0.90 (0.78, 1.04)	0.87 (0.75, 1.07)
VACS Risk Score greater than mean (vs. less than mean)	0.87 (0.81, 0.95)	0.78 (0.72, 0.85)

*Odds ratios come from a repeated measures logistic regression model adjusted for number of concomitant medications, age, race, alcohol abuse, drug abuse, major depression diagnosis, adherence and viral load suppression lagged to previous visit, calendar year, presence of a non-AIDS comorbidity, AIDS diagnosis, number of antiretrovirals; ^Reference group for race is black; reference group for number of concomitant medications:<2

Figure 4.1A. Number of concomitant medications used over time in the MACS (2001-2011)

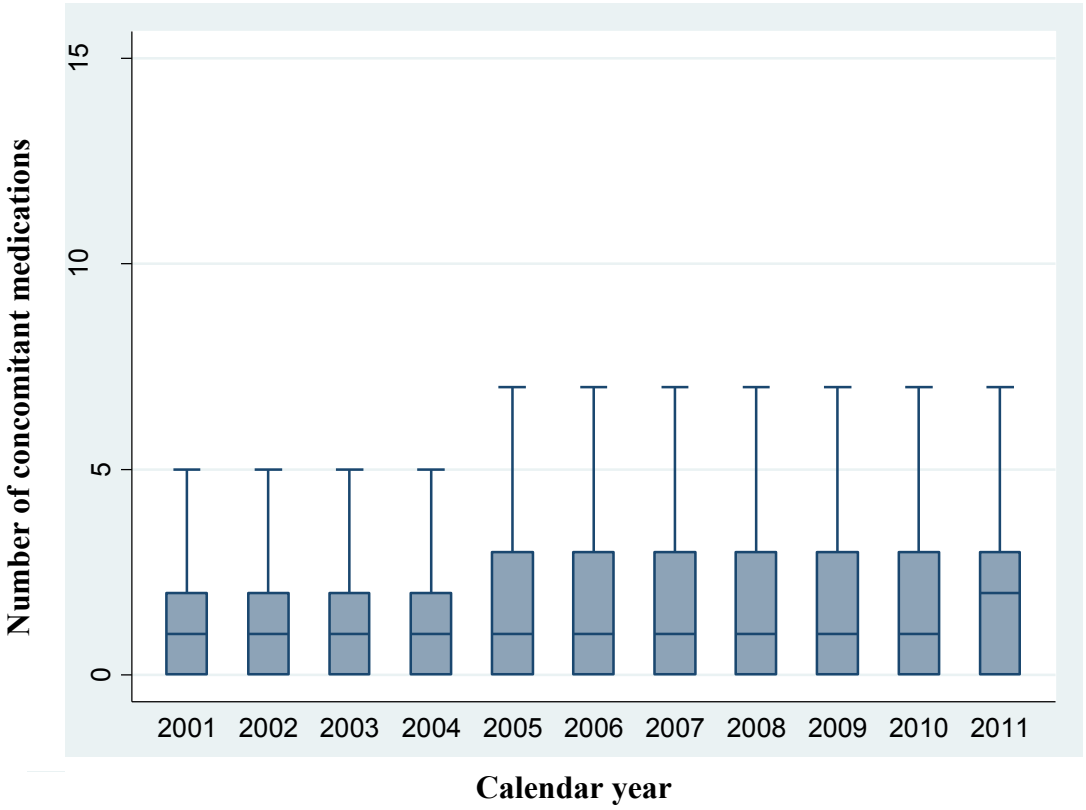


Figure 4.1B. Number of concomitant medication used over time in the VACS (2001-2010)

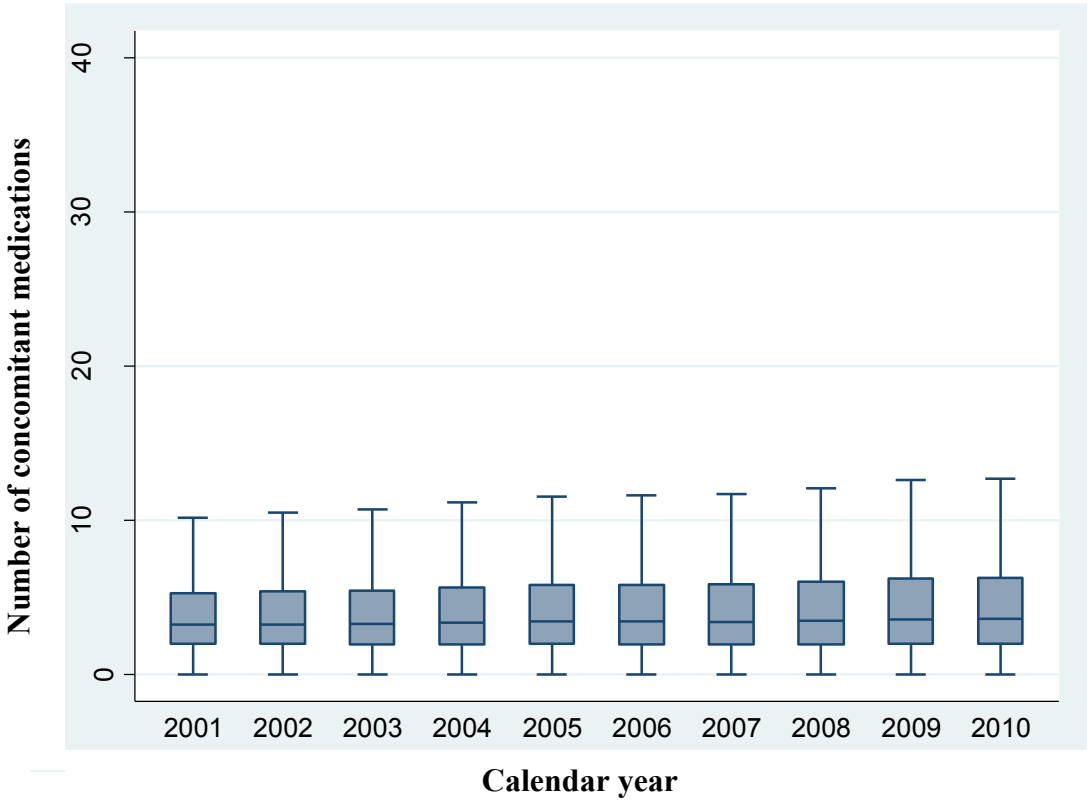


Figure 4.2A. Number of concomitant medications used by adherence category in the MACS (2006-2011)

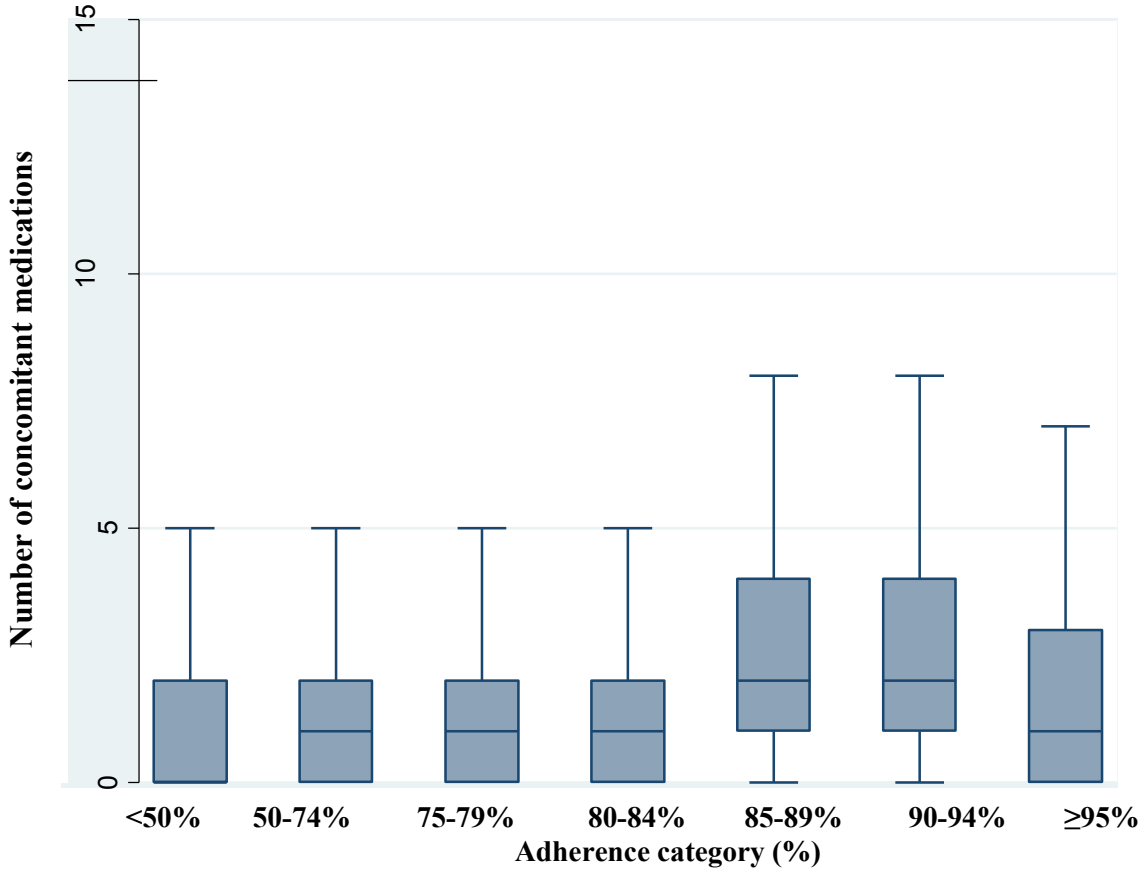


Figure 4.2B. Concomitant medication use by HAART adherence category in the VACS (2006-2010)

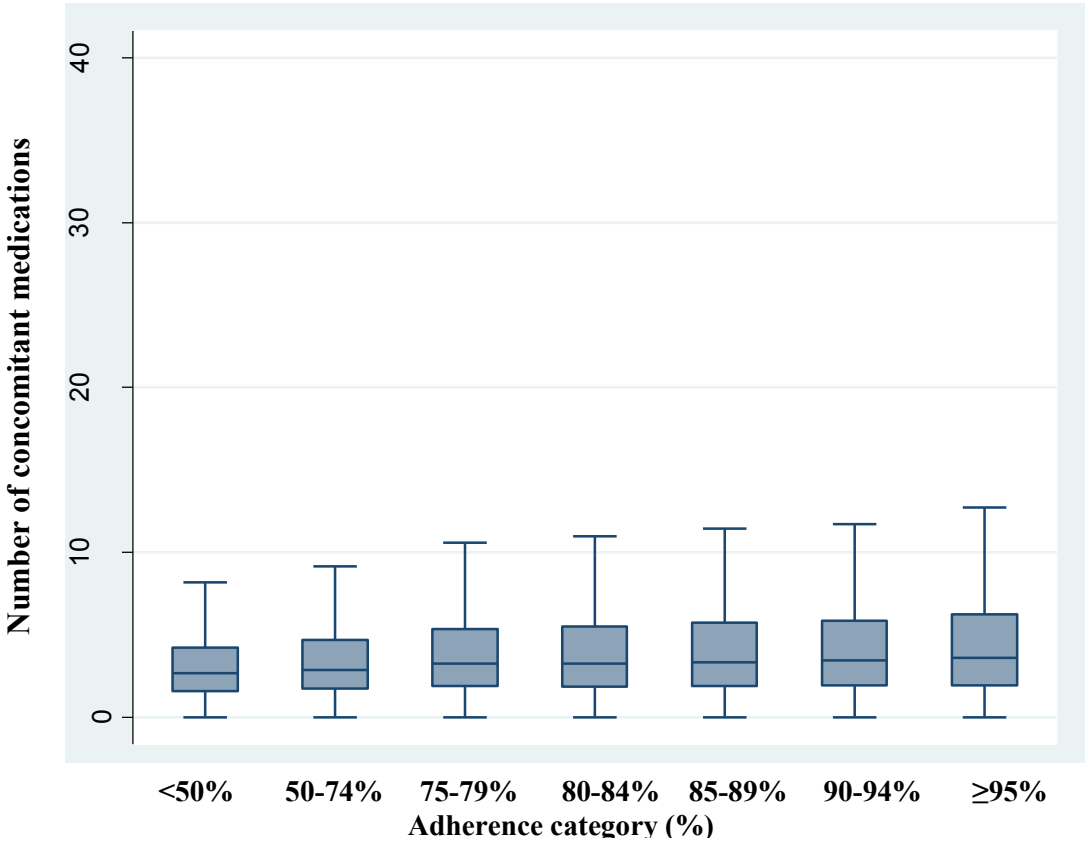
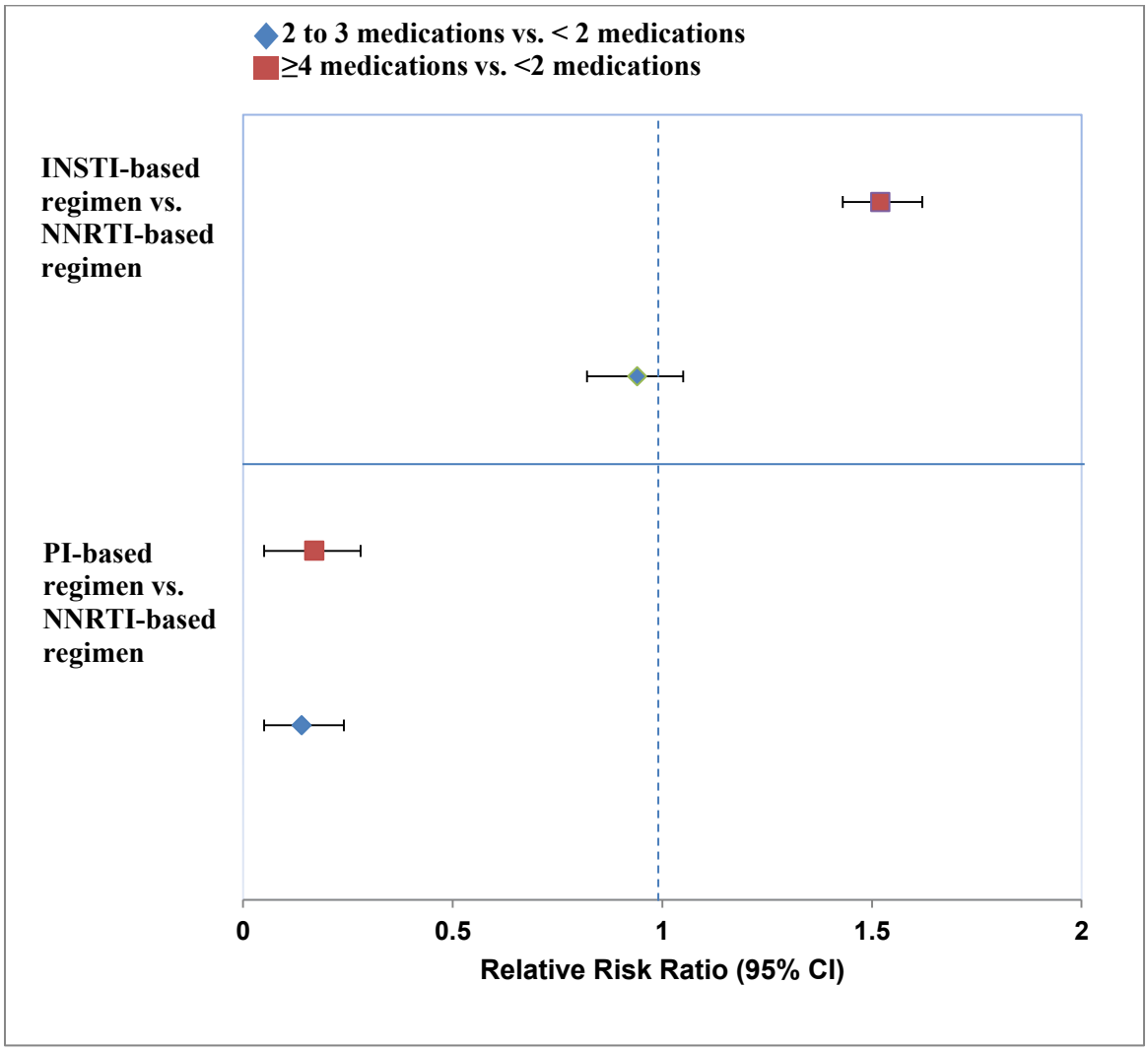
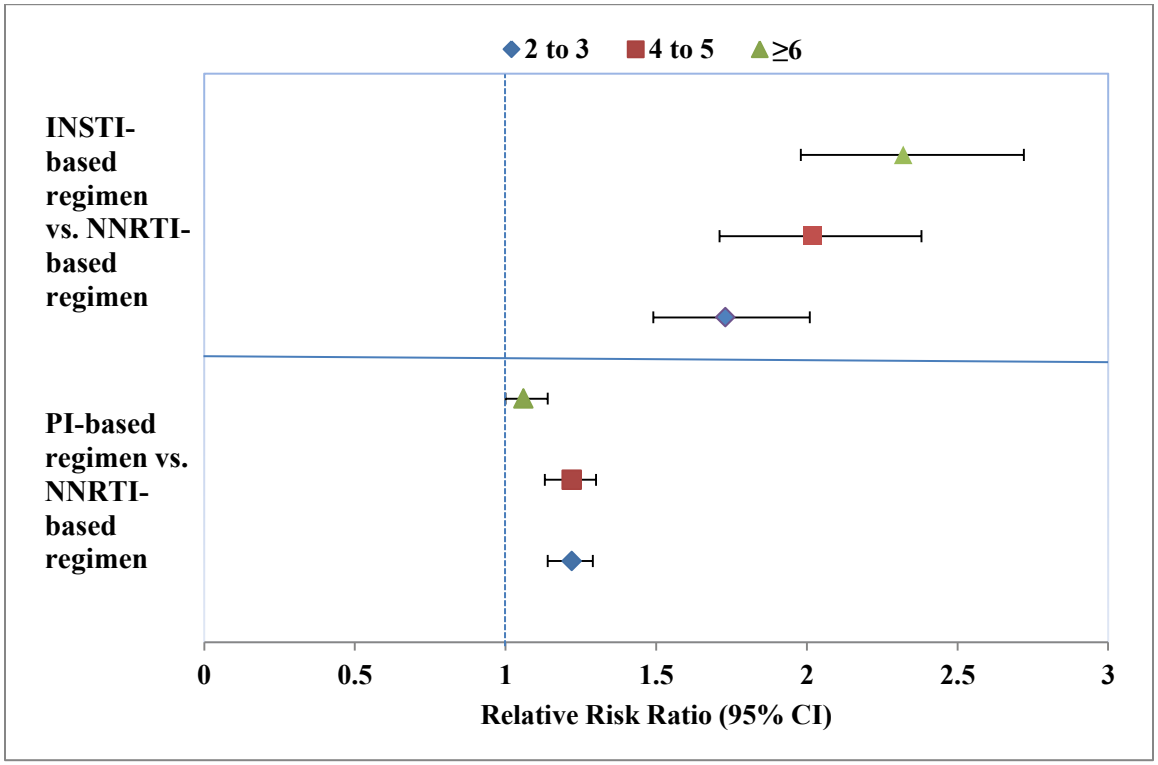


Figure 4.3A. Association between HAART regimen type and number of concomitant medications in the MACS (2006-2011)



Relative risk ratio estimates come from a multinomial regression model with HAART regimen type as outcome (NNRTI-based regimen as reference) and the number of concomitant medications as the main exposure variable (less than 2 medications as reference category), adjusted for age, race, smoking, alcohol use, non-injection drug use, minimum optimal adherence, baseline visit (before or after 2001), and viral load suppression lagged to the previous visit

Figure 4.3B. Association between HAART regimen type and number of concomitant medications in the VACS (2006-2010)



Relative risk ratio estimates come from a multinomial regression model with HAART regimen type as outcome (NNRTI-based regimen as reference) and number of concomitant medications as the main exposure variable (less than 2 medications as reference category), adjusted for age, race, alcohol abuse, drug abuse, major depression diagnosis, adherence lagged to previous year, geographical location, VACS Risk Score

Figure 4.4A. Use of concomitant medications for chronic non-AIDS conditions (2001-2011) by therapeutic class in the MACS (N person-years=14,413)

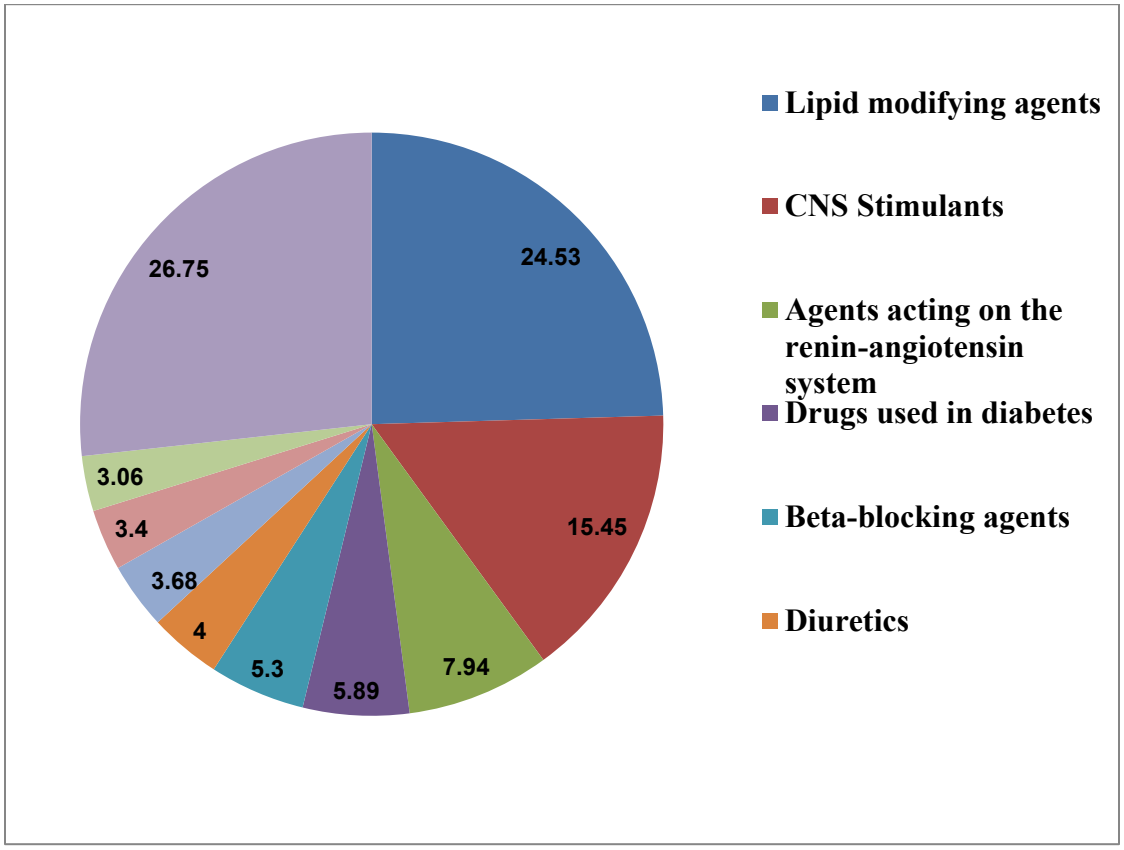


Figure 4.4B. Use of concomitant medications for chronic non-AIDS conditions (2001-2010) by therapeutic class in the VACS (N person-years=496,293)

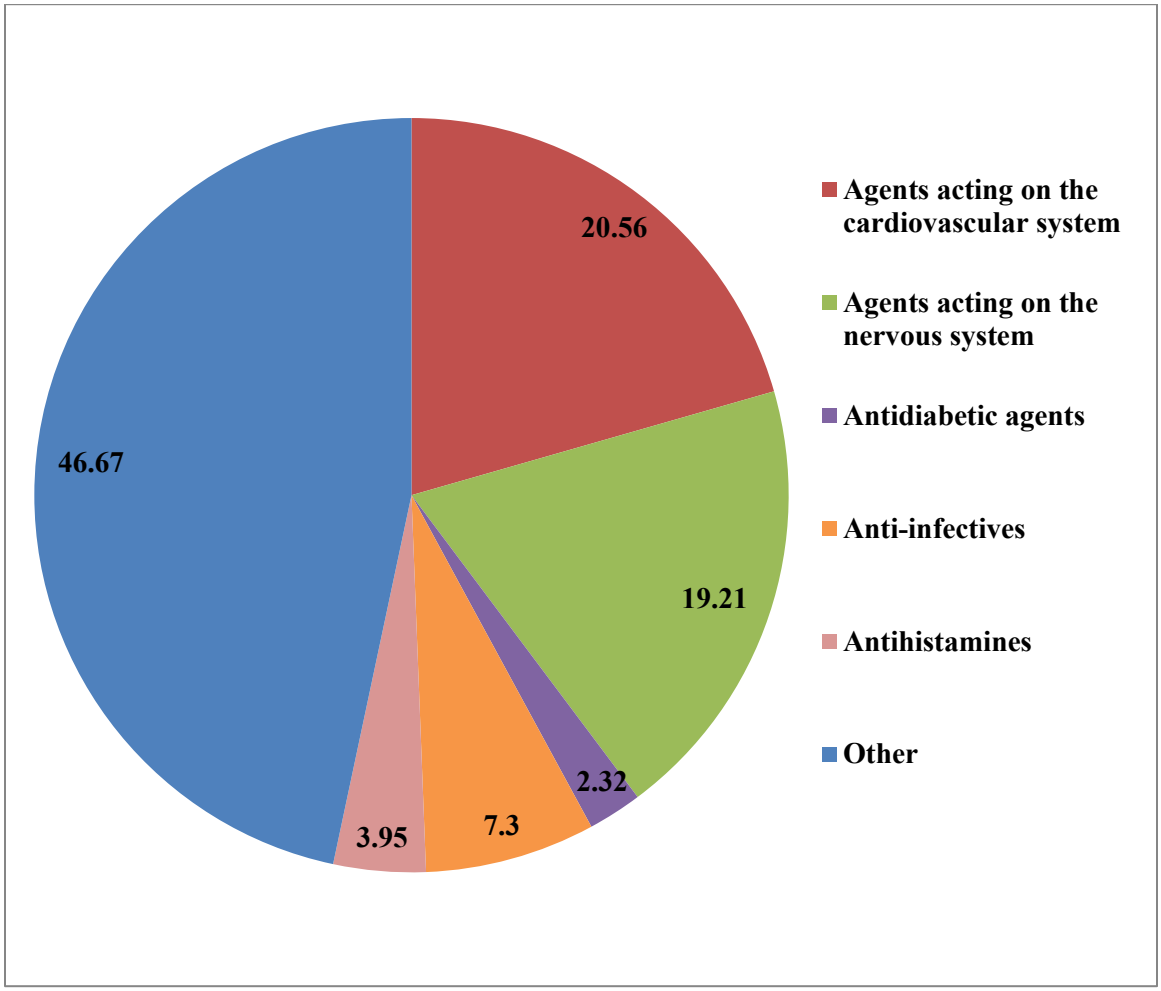


Figure 4.5A. Minimum optimal adherence according to concomitant medication use by age in the MACS (2006-2011)

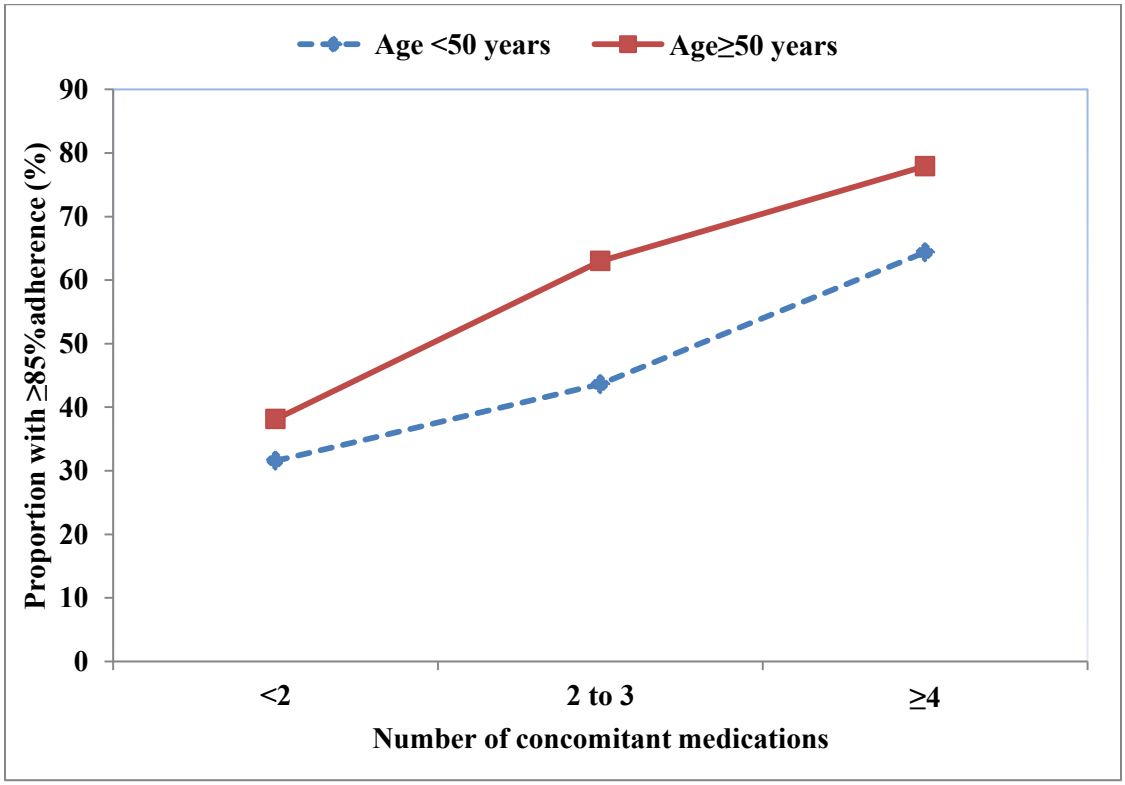
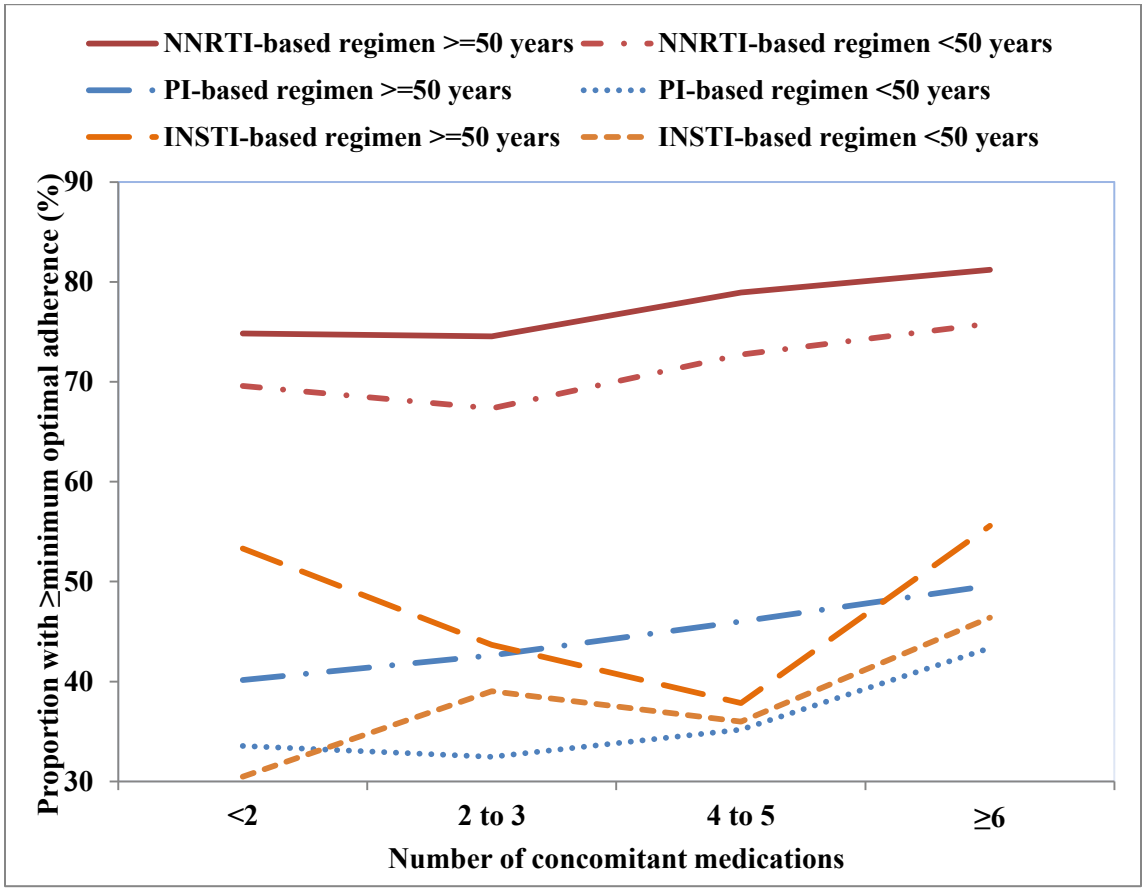
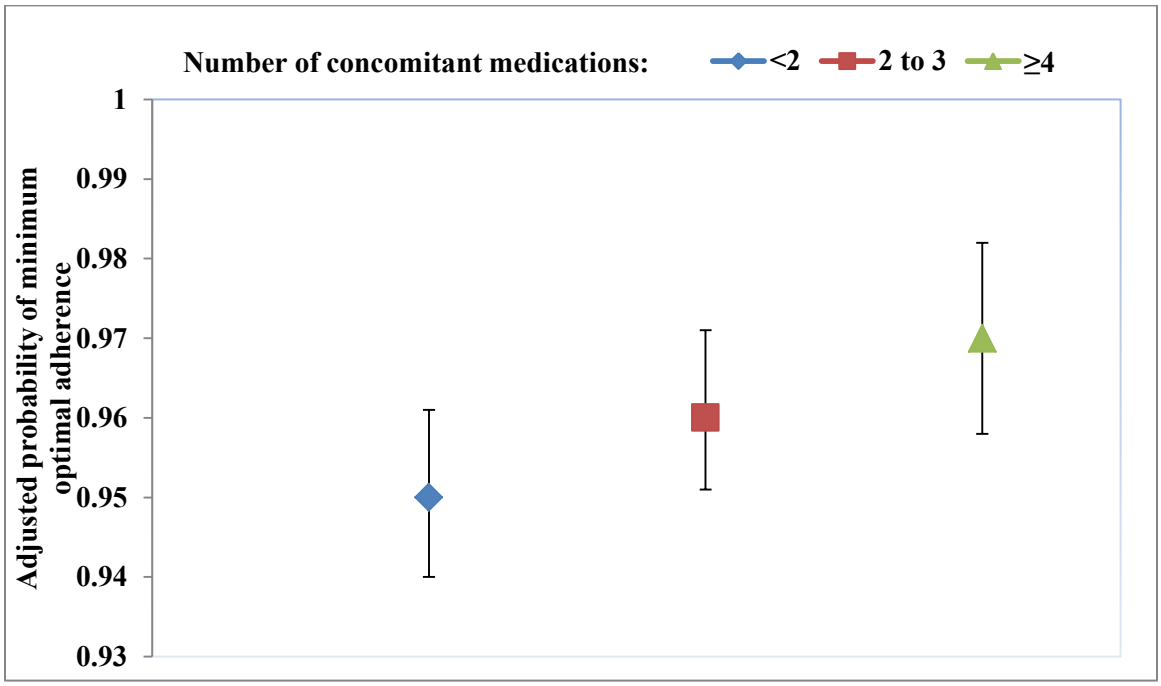


Figure 4.5B. Minimum optimal adherence according to concomitant medication use by age in the VACS (2006-2010)



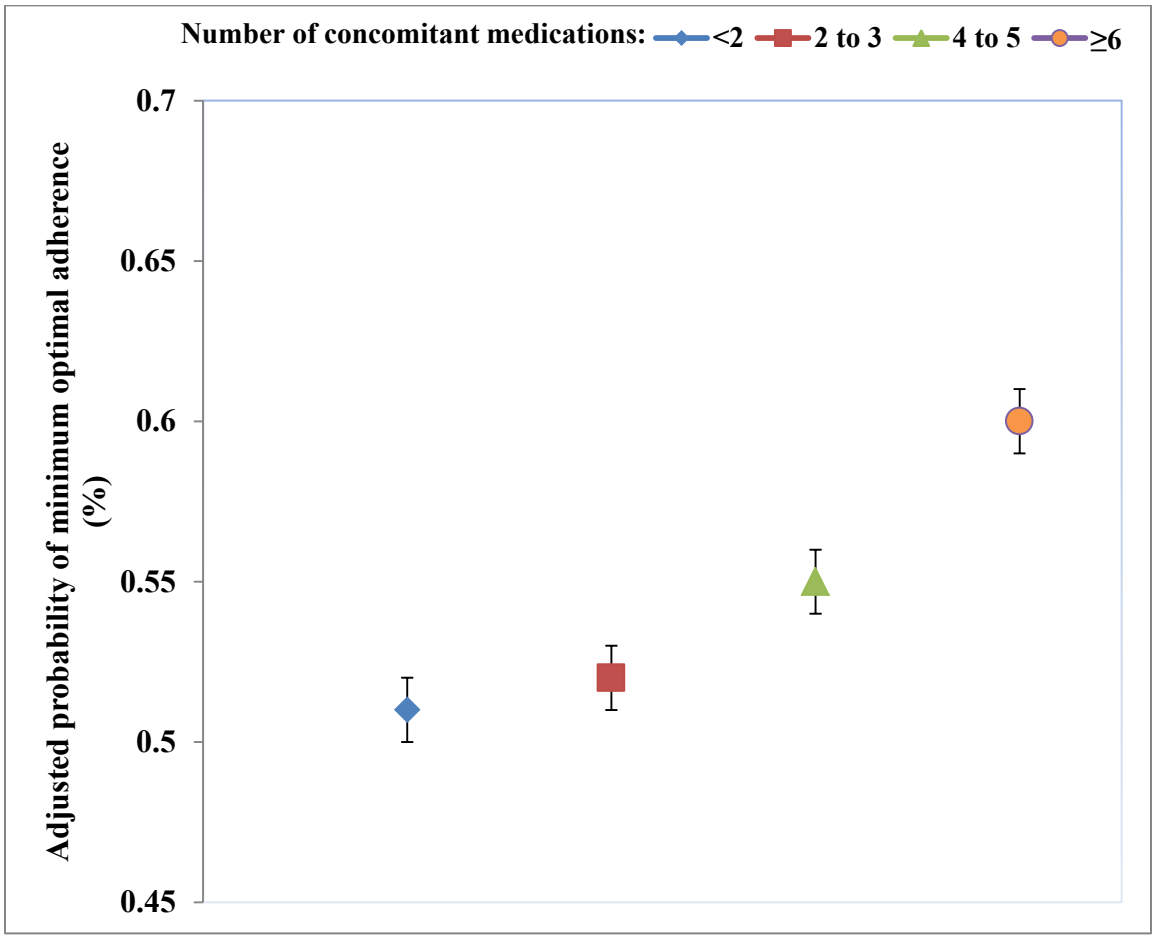
*Minimum optimal adherence for NNRTI-based regimens: ≥85%; Minimum optimal adherence for PI-based and INSTI-based regimens: ≥95%

Figure 4.6A. Adjusted probability of minimum optimal adherence by concomitant medication use over time in the MACS (2006-2011)



*Adjusted probability comes from a repeated measures logistic regression model adjusted for age, race, insurance status, alcohol use, smoking, non-injection drug use, injection drug use, depression, type of HAART, viral load suppression (lagged to previous visit)

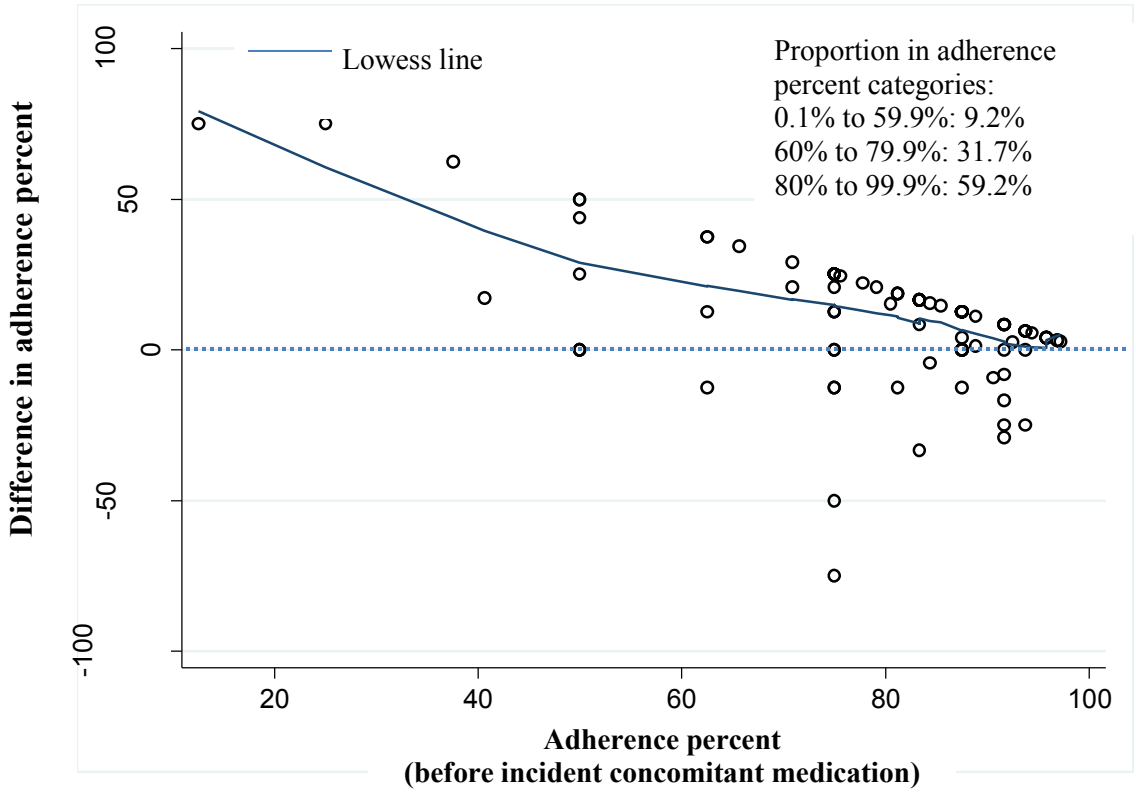
Figure 4.6B. Adjusted probability of minimum optimal adherence by concomitant medication use over time (2006-2010)



*Adjusted probability comes from a repeated measures logistic regression model adjusted for age, race, alcohol abuse, drug abuse, major depression diagnosis, adherence and viral load suppression lagged to previous visit, calendar year, presence of a non-AIDS comorbidity, AIDS diagnosis, number of antiretrovirals

Figure 4.7A. Change in adherence before incident use of a concomitant medication and adherence at incident visit in the MACS (2001-2011)

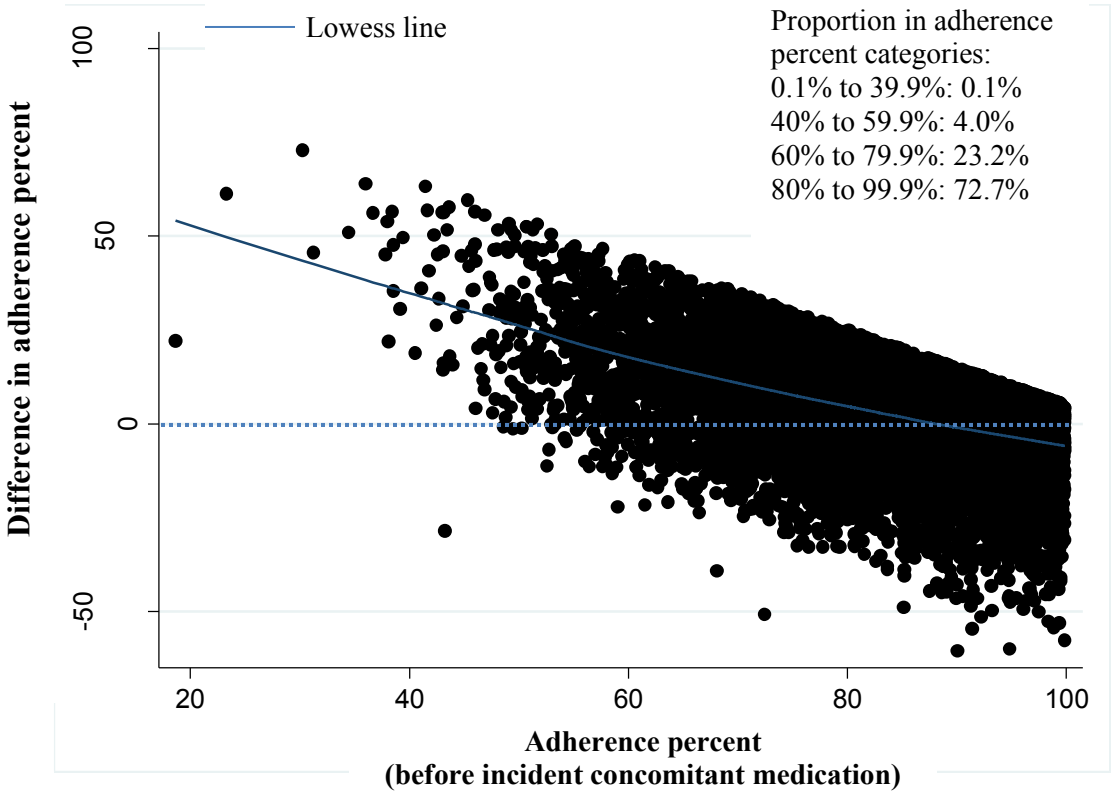
N= 120



*X-axis: adherence percent at the visit before the incident visit; Y-axis: difference in adherence between the incident visit and the previous visit; **only persons at the visit before the incident visit; excluding persons with only one visit or a visit interval greater than 1 year and excluding persons with adherence at the visit before the incident visit not equal to 0 or 100%

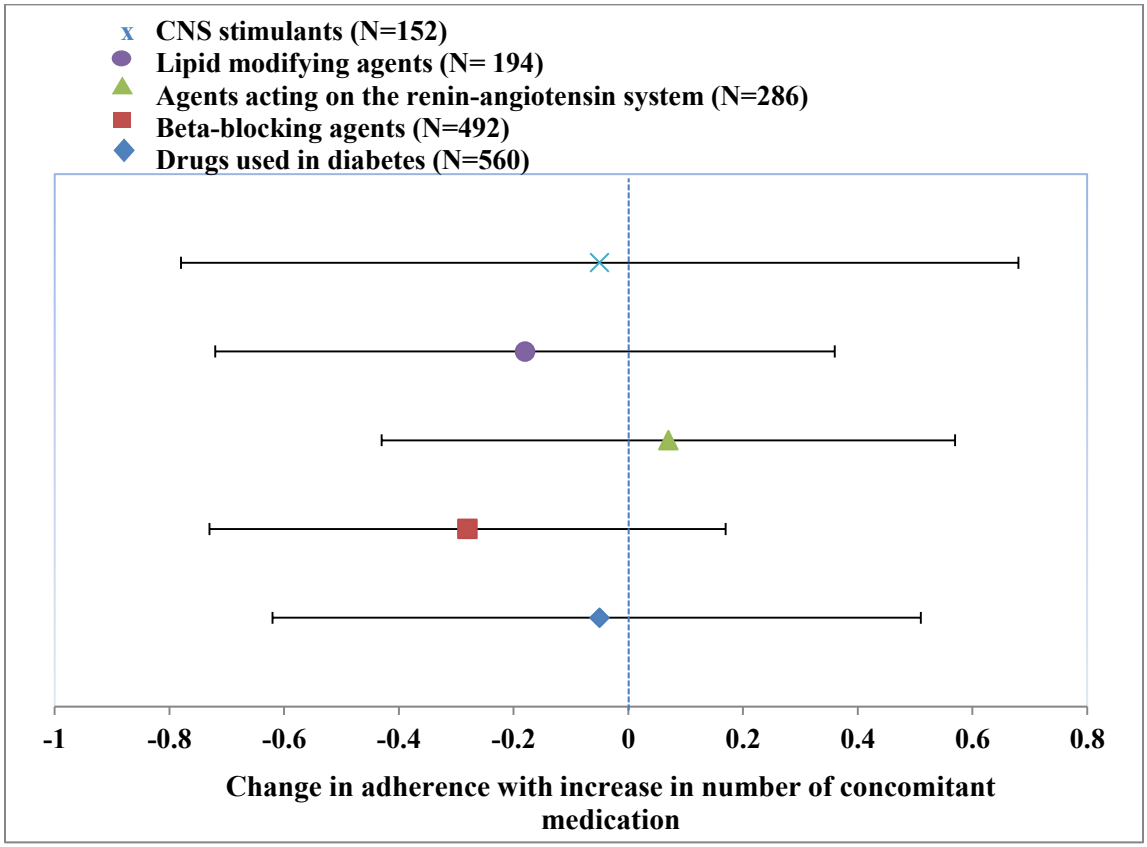
Figure 4.7B. Change in adherence before incident use of a concomitant medication and adherence at incident visit in the VACS (2001-2010)

N=11,177



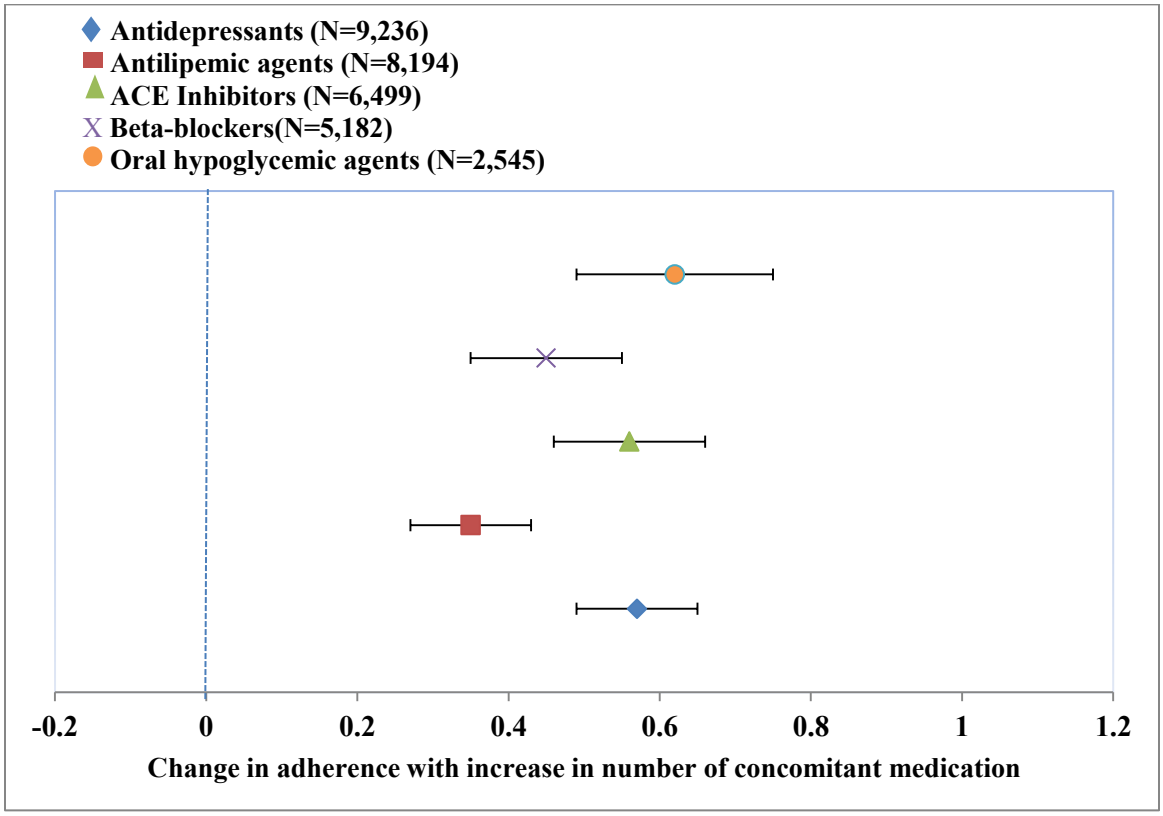
*X-axis: adherence percent at the visit before the incident visit; Y-axis: difference in adherence between the incident visit and the previous visit; **only persons at the visit before the incident visit; excluding persons with only one visit or a visit interval greater than 1 year and excluding persons with adherence at the visit before the incident visit not equal to 0 or 100%

Figure 4.8A. Adherence according to number of medications used in populations representing incident use among those using at least one drug from medication classes in the MACS (2001-2011)



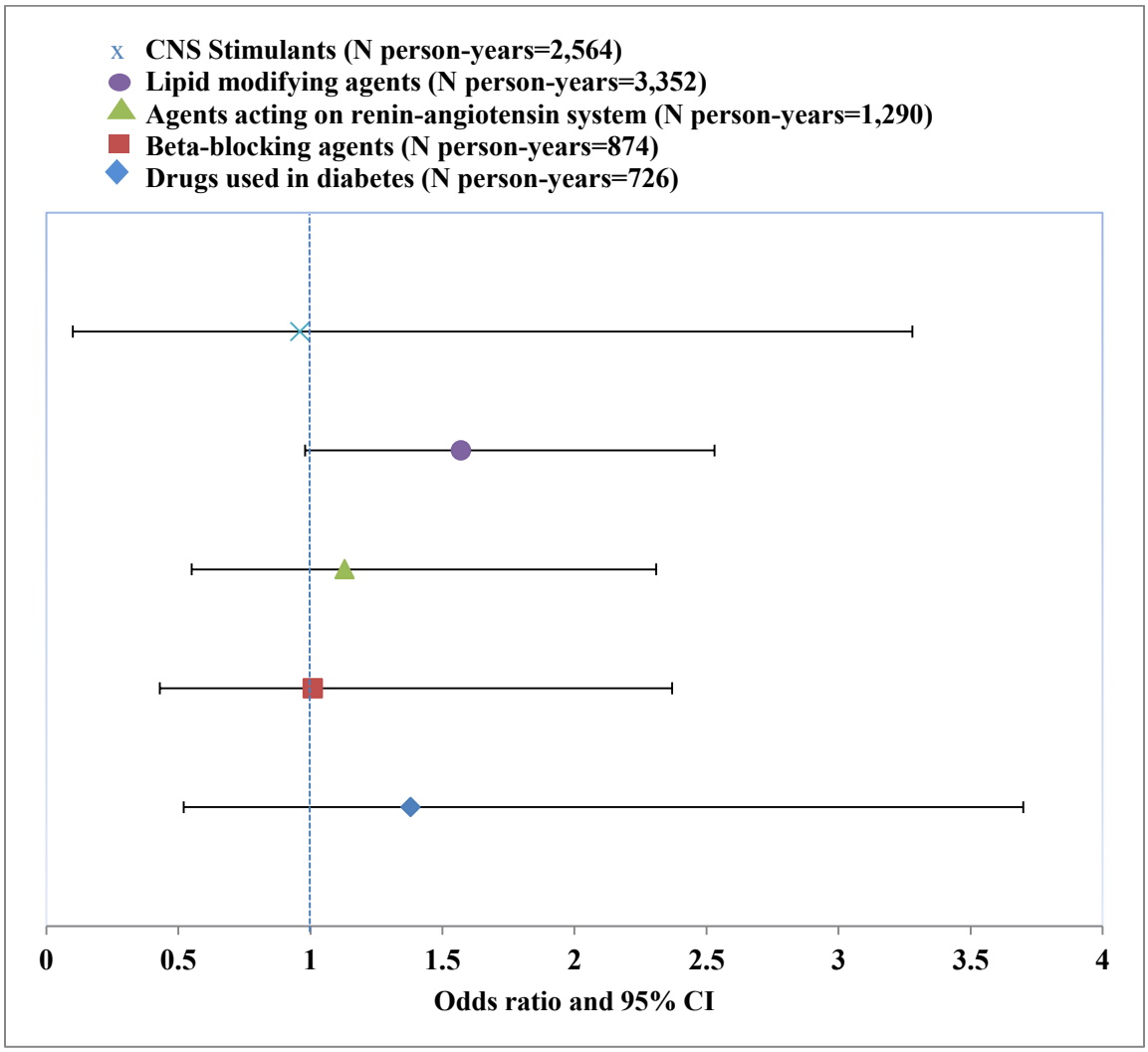
Estimates come from a linear regression models with adherence percent as outcome and concomitant medications as a continuous exposure adjusted for age, race, alcohol use, smoking, income, non-injection recreational drug use, number of comorbidities, type of HAART regimen

Figure 4.8B. Adherence according to number of medications used in populations representing incident use among those using at least one drug from medication classes in the VACS (2001-2010)



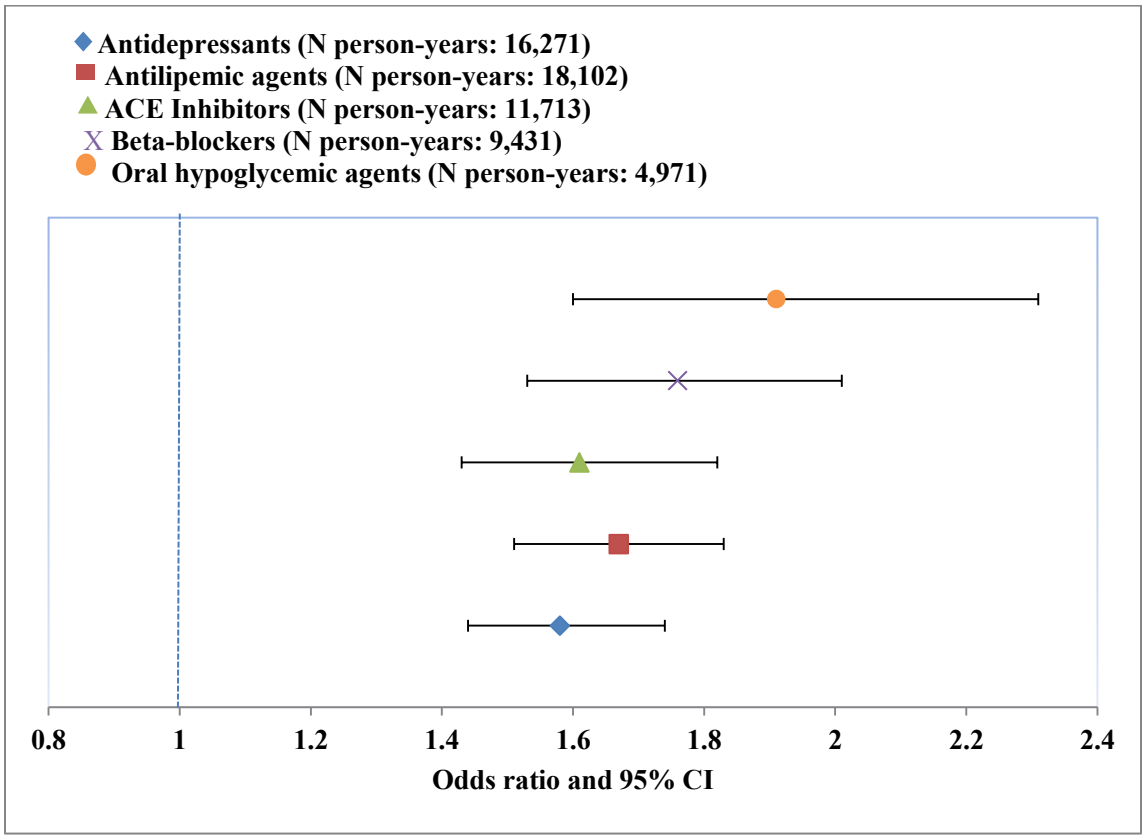
Estimates come from a linear regression model with adherence percent as outcome and concomitant medications as a continuous exposure adjusted for age, race, alcohol abuse, drug abuse, major depression diagnosis, type of HAART regimen, VACS Risk Score

Figure 4.9A Odds of minimum optimal adherence according to number of medications used in populations among those using at least one drug from medication classes in the MACS (2001-2011)



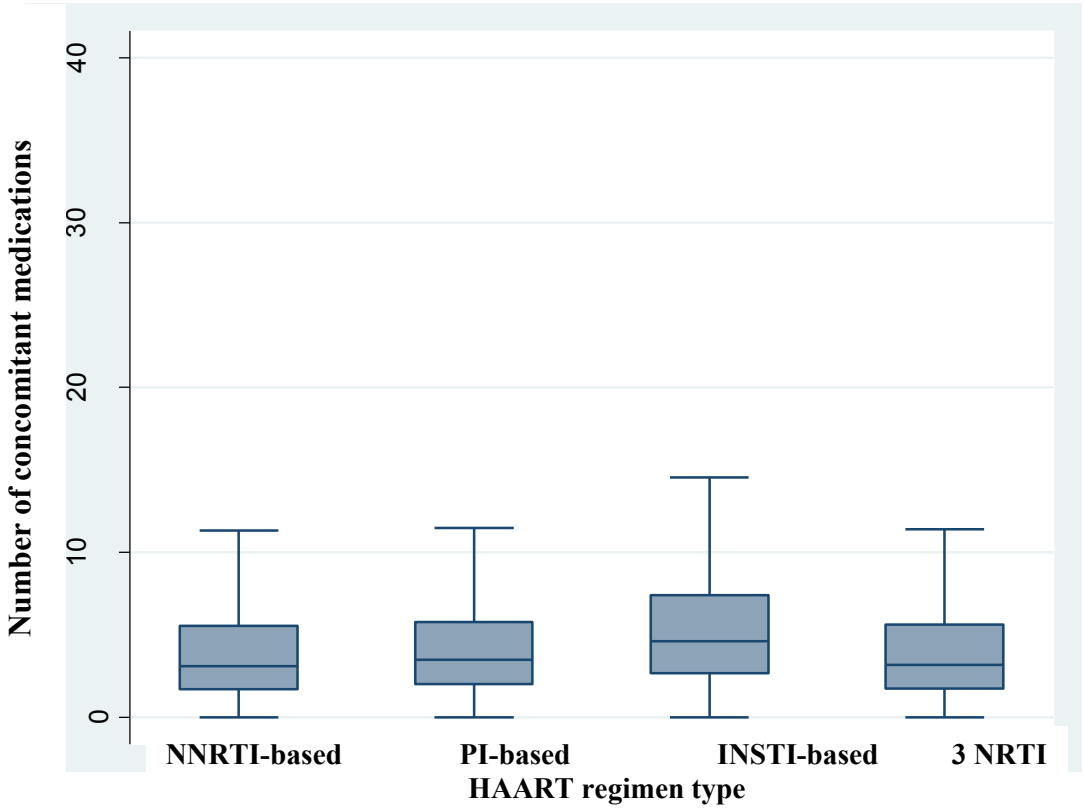
Odds ratios and 95% CI come from repeated measures logistic regression models with the minimum optimal adherence cutoff of 85% as the outcome and exposure dichotomized at mean concomitant medication use, adjusted for age, alcohol use, smoking, non-injection recreational drug use, income, type of HAART regimen, number of comorbidities

Figure 4.9B. Odds of minimum optimal adherence according to number of medications used in populations among those using at least one drug from medication classes in the VACS (2001-2010)

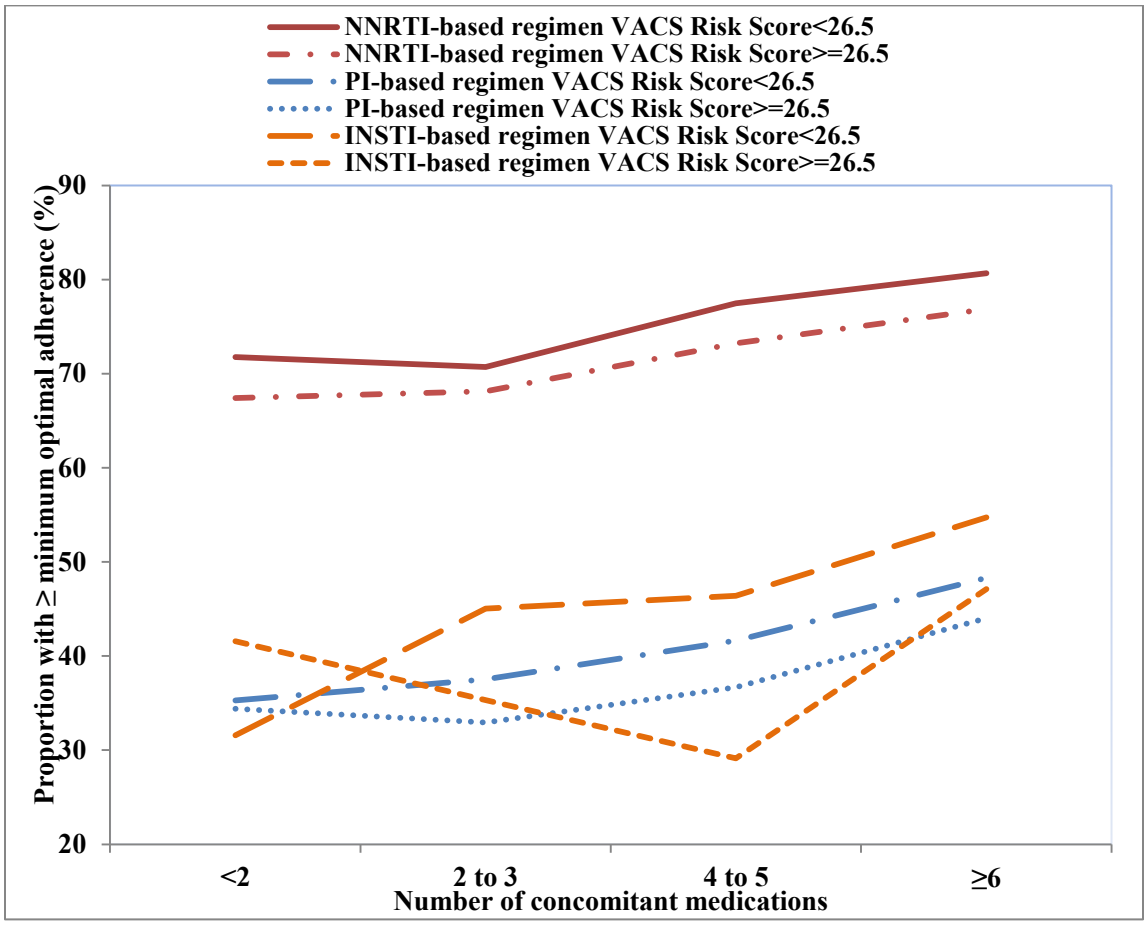


Odds ratios and 95% CI come from repeated measures logistic regression models with the minimum optimal adherence cutoff as the outcome and exposure dichotomized at mean concomitant medication use, adjusted for age, race, alcohol abuse, drug abuse, major depression diagnosis, type of HAART regimen, VACS Risk Score; minimum optimal cutoff depends on the type of HAART regimen used: NNRTI: ≥85%, PI: ≥95%; INSTI: ≥95%

Appendix Figure 4.1. Concomitant medication use by HAART regimen type in the VACS (2006-2010)

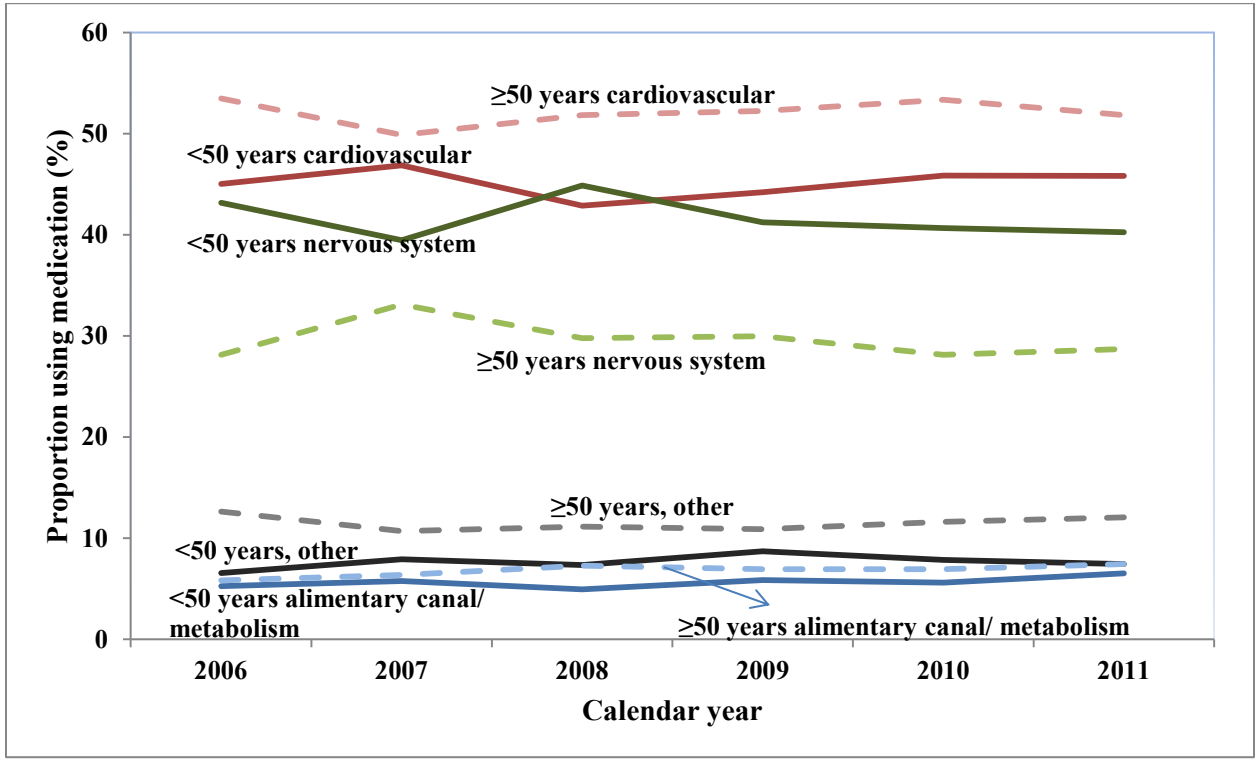


Appendix Figure 4.2. Adherence according to number of concomitant medications used by mean VACS risk score in the VACS (2006-2010)



*Minimum optimal adherence for NNRTI-based regimens: ≥85%; Minimum optimal adherence for PI-based and INSTI-based regimens: ≥95% **mean VACS Risk Score=26.5

Appendix Figure 4.3. Use of concomitant medications for chronic non-AIDS conditions (2006-2011) by anatomical/main group by age in the MACS (N person-years=14,413)



Appendix 4.1. List of pharmacological classes used in the MACS according to WHO ATC

Main Group	Therapeutic group	Pharmacologic group
Alimentary tract and metabolism		
	Bile and liver therapy	
	Drugs used in diabetes	1. Insulins and analogues
		2. Blood glucose lowering drugs, excluding insulins
		3. Other drugs used in diabetes
Blood and blood forming organs		
	Antithrombotic agents	
	Antihemorrhagics	
	Antianemic preparations	
	Other hematological agents	
Cardiovascular system		
	Cardiac therapy	A. Cardiac glycosides
		B. Antiarrhythmics, class I and III
		C. Cardiac stimulants excluding cardiac glycosides
		D. Vasodilators used in cardiac diseases
		E. Other cardiac preparations
	Antihypertensives	A. Antiadrenergic agents, centrally acting
		B. Antiadrenergic agents, ganglion-blocking
		C. Antiadrenergic agents, peripherally acting
		D. Arteriolar smooth muscle, agents acting on
		K.Other antihypertensives

Main Group	Therapeutic group	Pharmacologic group
		L. Antihypertensives and diuretics in combination
		N. Combinations of antihypertensives
	Diuretics	A. Low-ceiling diuretics, thiazides
		B. Low-ceiling diuretics, excluding thiazides
		C. High-ceiling diuretics
		D. Potassium-sparing agents
		E. Diuretics and potassium-sparing agents in combination
		X. Other diuretics
	Peripheral vasodilators	
	Vasoprotectives	B. Antivaricose therapy
		C. Capillary stabilizing agents
	Beta blocking agents	A. Beta blocking agents
		B. Beta blocking agents and thiazides
		C. Beta blocking agents and other diuretics
		D. Beta blocking agents, thiazides and other diuretics
		E. Beta blocking agents and vasodilators
		F. Beta blocking agents and other antihypertensives
	Calcium channel blockers	C.Selective calcium channel blockers with mainly vascular effects
		D. Selective calcium channel blockers with direct cardiac

Main Group	Therapeutic group	Pharmacologic group
		effects E. Non-selective calcium channel blockers G. Calcium channel blockers and diuretics
	Agents acting on the renin-angiotensin system	A. ACE inhibitors, plain B. ACE inhibitors, combinations C. Angiotensin II antagonists, plain D. Angiotensin II antagonists, combinations X. Other agents acting on the renin-angiotensin system
	Lipid modifying agents	*A.Plain* 1. HMG CoA 2. Fibrates 3. Bile acid sequestrants 4. Nicotinic acid derivatives 5. Other lipid modifying agents *B.Combinations* 1. HMG CoA reductase inhibitors in combination with other lipid modifying agents 2. HMG CoA reductase inhibitors, other combinations
Systemic hormonal prep		
	Pituitary and hypothalamic hormones and analogues *Corticosteroids for systemic use* *Thyroid therapy* *Pancreatic hormones*	

Main Group	Therapeutic group	Pharmacologic group
	Calcium homeostasis	
Antiinfectives for systemic use		
	Antimycobacterials	
	Antivirals for systemic use	
Antineoplastic and immunomodulating agents		
	Antineoplastic agents	
	Endocrine therapy	
	Immunostimulants	
	Immunosuppressants	
Musculo-skeletal system		
	Antiinflammatory and antirheumatic products	
	Muscle relaxants	
	Antigout preparations	
	Drugs for treatment of bone disease	
Nervous system		
	Antiepileptics	
	Anti-parkinson drugs	
	Psycholeptics	A. Antipsychotics
		B. Anxiolytics
		C. Hypnotics and sedatives
	Psychoanaleptics	A. Antidepressants
		B. Psychostimulants
		C. Psycholeptics and psychoanaleptics
		D. Anti-dementia drugs
	Other nervous system drugs	

Appendix 4.2. List of pharmacological classes used in the VACS according to VA Class Index

VA class	
am110 penicillin-g related penicillins	cn101 opioid analgesics
am111 penicillins,amino derivatives	cn102 opioid antagonist analgesics
am112 penicillinase-resistant penicillins	cn103 non-opioid analgesics
am115 cephalosporin 1st generation	cn105 antimigraine agents
am116 cephalosporin 2nd generation	cn204 local anesthetics,injection
am117 cephalosporin 3rd generation	cn300 sedatives/hypontics
am118 cephalosporin 4th generation	cn301 barbituric acid derivative sedatives/hypnotics
am119 beta-lactams antimicrobials,other	cn302 benzodiazepine derivative sedatives/hypnotics
am200 erythromycins/macrolides	cn309 sedatives/hypnotics,other
am250 tetracyclines	cn400 anticonvulsants
am300 aminoglycosides	cn500 antiparkinson agents
am350 lincomycins	cn550 antivertigo agents
am500 antituberculars	cn601 tricyclic antidepressants
am550 methenamine salts antimicrobials	cn602 monamine oxidase inhibitor antidepressants
am600 nitrofurans antimicrobials	cn609 antidepressants,other
am650 sulfonamide/related antimicrobials	cn701 phenothiazine/related antipsychotics
am700 antifungals	cn709 antipsychotics,other
am800 antivirals	cn750 lithium salts
am900 anti-infectives,other	cn801 amphetamines
am119 beta-lactams antimicrobials,other	cn802 amphetamine like stimulants
am200 erythromycins/macrolides	cn809 cns stimulants,other
am250 tetracyclines	cn900 cns medications,other

VA class	
am300 aminoglycosides	cv050 digitalis glycosides
am350 lincomycins	cv100 beta blockers/related
am500 antituberculars	cv150 alpha blockers/related
am550 methenamine salts antimicrobials	cv200 calcium channel blockers
am600 nitrofurans antimicrobials	cv250 antianginals
am650 sulfonamide/related antimicrobials	cv300 antiarrhythmics
am700 antifungals	cv350 antilipemic agents
am800 antivirals	cv400 antihypertensive combinations
am900 anti-infectives,other	cv490 antihypertensives,other
hs051 glucocorticoids	cv500 peripheral vasodilators
hs052 mineralocorticoids	cv701 thiazides/related diuretics
hs100 androgens/anabolics	cv702 loop diuretics
hs200 contraceptives,systemic	cv703 carbonic anhydrase inhibitor diuretics
hs300 estrogens	cv704 potassium sparing/combinations diuretics
hs400 gonadotropins	cv709 diuretics,other
hs500 blood glucose regulation agents	cv800 ace inhibitors
hs501 insulin	cv805 angiotensin ii inhibitor
hs502 oral hypoglycemic agents,oral	cv806 direct renin inhibitor
hs503 antihypoglycemics	cv900 cardiovascular agents,other
hs600 parathyroid	re101 anti-inflammatories,inhalation
hs701 anterior pituitary	re102 bronchodilators,sympathomimetic,inhalation
hs702 posterior pituitary	re103 bronchodilators,sympathomimetic,oral
hs800 progestins	re104 bronchodilators,xanthine-derivative

VA class	
hs851 thyroid supplements	re105 bronchodilators,anticholinergic
hs852 antithyroid agents	re108 antiasthma,antileukotrienes
hs875 prostaglandins	re109 antiasthma,other
hs900 hormones/synthetics/modifiers,other	re200 decongestants,systemic
	re301 opioid-containing antitussives/expectorants
	re302 non-opioid-containing antitussives/expectorants
	re400 mucolytics
	re501 antihistamine/decongestant
	re503 antihistamine/decongestant/expectorant
	re507 antihistamine/antitussive
	re513 decongestant/antitussive/expectorant
	re516 decongestant/expectorant
	re599 cold remedies,other
	re900 respiratory agents,other

Appendix 4.3. Example showing the calculation of the total mean number of non-ART long-term medications received for each patient in the VACS

$$\frac{\sum_{non-ARVs}(Medication\ refilled) * (Number\ of\ days\ in\ refill)}{Number\ of\ days\ in\ the\ year\ when\ at\ least\ one\ medication\ for\ a\ non\text{-}AIDS\ condition\ was\ used}$$

Consider patient X fills her prescriptions between October 1, 2005 and September 30, 2006. She fills prescriptions for Lipitor 20mg on October 5, 2005 for 90 days, returns on January 10, 2006 to refill the prescription for 90 days, on April 14, 2006 to refill for 90 days, and on July 15, 2006 to refill for 90 days. She also refills a prescription for Prandin 1mg on December 2, 2005 for 90 days, returns on March 5, 2006 to refill for 90 days, and on June 15, 2006 to refill for 90 days. The total mean number of non-ART long-term medications can be calculated as follows:

	Dates	**Number of days refilled**	**Days without medication**	**Days without any medication**
Lipitor 20mg	Oct 1, 2005 to Jan 3, 2006	90		
	Jan 10, 2006 to Apr 10, 2006	90	Jan 4 through Jan 9= 6	0

	Dates	Number of days refilled	Days without medication	Days without any medication
	Apr 14, 2006 to Jul 13, 2006	90	Apr 11 to Apr 13=3	0
	Jul 15, 2006 to Oct 13, 2006	90	Jul 14=1	0
Prandin 1mg	Dec 2, 2005 to Mar 2, 2006	90	Oct 1 to Dec 2= 62	0
	Mar 5, 2006 to May 31, 2006	90	Mar 3 to Mar 4=2	0
	Jun 15, 2006 to Sept 13, 2006	90	Jun 1 to Jun 14=14	0
				Total days without any medication =0

Since Lipitor 20mg and Prandin 1mg were refilled for a total of 7 times that year, numerator=*90*7= 630*

Since the number of days without any medication=0, the denominator (number of days when at least one drug was used) = *364*

Therefore, the total mean number of non-ART long-term medications received for patient X between 2005 and 2006 = *630/ 364 = 1.73*

CHAPTER FIVE

Conclusions

Summary of findings

This dissertation generates essential knowledge regarding adherence to HAART in the current era of treatment. We determined the minimum needed adherence level to HAART for viral load suppression in two distinct risk groups of HIV-infected persons in the US – MSM and IDU. Further, we evaluated whether this minimum optimal adherence cutoff was different by HAART regimen type using a large observational cohort of HIV-infected veterans presenting at Veterans Health Administration centers nationwide. Notwithstanding the simplification and enhancement in safety and efficacy of HAART formulations, and the associated improvement in adherence and viral load suppression over time, HIV-infected persons now use concomitant medications for chronic non-AIDS conditions, which has led to increased treatment complexity. We examined whether the increased treatment complexity was a barrier in adhering to HAART regimens in the current era of treatment.

As shown in Chapter 2, we evaluated the minimum optimal adherence to HAART using self-reported adherence, and data in laboratory tests and physical examinations from two longitudinal interval cohort studies of HIV-infected persons in the US - the MACS and the ALIVE. We found that the proportion reporting high levels of adherence (≥95%) increased over time ($p_{trend}<0.001$) in both cohorts. Even among those reporting less than 95% adherence, the proportion with suppressed viral load increased over time ($p_{trend}<0.001$) in both cohorts. Overall, the most commonly used HAART regimen between 2001 and 2011 was PI-based in both cohorts. In the MACS, levels of adherence as low as 80% were sufficient for viral load suppression, with over 80% of the population being suppressed, and the odds of suppression not being significantly different than that

at adherence levels ≥ 95% adherence (OR: 1.43 (0.61, 3.33)). In the ALIVE, less than 80% were suppressed even at near perfect levels of adherence, and the odds of suppression at adherence <95% was lower than that at adherence ≥95%. We therefore did not observe a minimum optimal adherence cutoff lower than 95% in the ALIVE. However, since we used two cohorts for analysis, we were able to identify several targets for adherence interventions, particularly in the IDU population based on a comparison of the results with the MSM group such as substance use, the use of older HAART regimens, and gaps in treatment and factors related to gaps in treatment such as incarceration, homelessness and low income.

As shown in Chapter 3, we determined the minimum optimal adherence to specific HAART regimens using pharmacy refill data, clinical and laboratory records from the VACS virtual cohort. Similar to our findings in the MACS and the ALIVE, the proportion reporting high levels of adherence, and the proportion suppressed even among those with <95% adherence increased over time. At the end of 2010, almost 30% of the study population used NNRTI-based single pill regimens, and 11% used INSTI-based regimens. Compared to PI-based and INSTI-based regimens, the use of NNRTI-based regimens was associated with a higher proportion achieving HIV RNA suppression with near-perfect levels of adherence. Among NNRTI users, the odds of HIV RNA suppression did not significantly differ compared to that with ≥95% adherence at adherence levels lower than 95% (OR: 85-89% adherence: multi-pill users: 0.82 (0.64,1.04) and 90-94% adherence: 1.10 (0.89, 1.36)). Conversely, we found that users of PI-based regimens were less likely to suppress virus at adherence levels lower than 95% (e.g., 90-94% adherence, OR: 0.88 (0.77, 0.99). This study, while conforming to our

findings from the MACS, shows that newer formulations i.e., NNRTI-based regimens are more forgiving in terms of effectiveness at lower levels of adherence than what was needed for earlier HAART formulations.

In Chapter 4, we showed results on the effect of increased treatment complexity due to chronic use of concomitant medications for non-AIDS conditions on adherence to HAART using data from the MACS and the VACS. The use of concomitant medications increased over time, and persons older than 50 years were more likely to use concomitant medications and achieve minimum optimal adherence in both cohorts. The use of more concomitant medications was associated with the use of INSTI-based regimens compared to other regimens. The most commonly used classes of non-AIDS medications in both cohorts were lipid modifying agents, beta-blockers, ACE inhibitors, and oral hypoglycemics. Longitudinally, the odds of achieving minimum optimal adherence increased with an increase in the number of concomitant medications in the MACS (≥4 vs. <2: 1.19 (0.75, 1.88)) and the VACS for both NNRTI-based regimens (≥6 vs. <2: 1.84 (1.57, 2.15)), and PI-based regimens (≥6 vs. <2: 1.97 (1.75, 2.23)). The results did not change even upon restricting the population to the use of specific pharmacologic classes of concomitant medications. This study sheds light on the need for continued emphasis on treatment management and adherence counseling in persons being treated for HIV and non-AIDS comorbidities, despite the improvements in HAART formulations, and the lower minimum cutoff for HIV RNA suppression in the current era of treatment.

Public health implications

This dissertation confirmed a lower cutoff of optimal adherence, and showed that polypharmacy did not negatively impact adherence to HAART in the current era of treatment. Prescribing HAART to HIV-infected persons early in the infection has been shown to have numerous benefits such as decreased progression of the disease to AIDS, and a lower probability of transmission of the disease to persons at risk.[1,2] Benefits of early HAART initiation even in persons with suboptimal adherence, have been found to outweigh the risks associated with non-adherence (i.e., long-term toxicity, drug resistance, and regimen changes).[3]

The levels of adherence needed for viral load suppression in different HIV-infected risk groups will enable providers of HIV care to better position their decisions regarding HAART use early in the course of infection. Our findings regarding poor retention to treatment, more barriers to adherence and lack of sustained virologic suppression in HIV-infected IDUs are consistent with previous studies looking at treatment-experienced IDU populations.[4,5,6] Early initiation of treatment with newer and improved regimens despite the barriers to adherence will lead to better treatment outcomes in the long-term. Providers can redistribute time and resources to persons with specific barriers to adherence, and provide comprehensive adherence-improvement interventions, adherence monitoring, and counseling sessions, especially to persons with mental illnesses, using non-prescription drugs and to IDUs. There is a need to focus on retaining these persons in care since we found a significant association between gaps in treatment and adherence.

The first-line regimens in ART-naïve persons have been discussed in Chapter 1. Our analysis was adjusted for factors that influenced the prescription of specific HAART regimens, and we observed that NNRTI-based regimens have better adherence overall, which could be attributed to ease of administration, and a lower minimum optimal cutoff of adherence compared to PI-based regimens and INSTI-based regimens. HIV-infected persons with poor access to care and barriers to adherence should be prescribed single pill regimens or INSTI-based regimens owing to ease of administration.

Even though polypharmacy did not have a negative impact on adherence to HAART, management of the medications taken by the patient at every visit is essential to prevent potential drug-drug interactions, and ensure medication safety. A recent study by Gleason et al[7] on polypharmacy in the older HIV-infected population suggested the need for "a thorough review of the medications", and "an annual medication reconciliation and a medical review at every visit". Some potential considerations during the review should include a check of whether the medications are on the list of inappropriate medications, and if necessary make appropriate dose changes, or change the drug used. Patients should be counseled and educated about all their comorbidities and their treatment. Studies have shown that knowledge of a disease and the consequence of not taking a medication regularly can impact adherence to medications.[8] While this partly explains our findings regarding the relationship between HAART adherence and polypharmacy, it is important for adherence to all their medications to be evaluated as part of the review. Although potential drug-drug interactions between ARV and non-ARV medications are well-documented, implementing and following a standardized protocol for the regular

monitoring of medications will ensure a strong evidence base for the management of treatment in HIV-infected persons in the current era of treatment.

Future directions

Although the findings from this dissertation will serve to guide providers in decision-making, future studies need to corroborate this work with studies involving other important HIV risk groups such as women. Given that women have lower rates of adherence,[9] and higher rates of virologic failure compared to men, the minimum optimal adherence cutoff in women may be different from that observed in other risk groups. We did not find significant differences in adherence and treatment outcomes by gender in our IDU population, and it may be worth focusing on women with lower rates of substance use.

A significant risk factor of poor adherence and virologic failure is gaps in treatment. Future work should evaluate the impact of interventions to improve retention in care, and if they changed the minimum optimal adherence to HAART in these individuals. Further, if persons with poor access to and retention in care were prescribed newer HAART medications, the impact of using these drugs on the minimum optimal adherence to HAART needs to be examined.

Switching regimens as a result of drug resistance and virologic failure is a relatively common occurrence in treatment-experienced HIV-infected persons.[10] Drug resistance is likely to impact the minimum optimal adherence to HAART, since virological suppression may not happen despite high levels of adherence. We were not able to measure drug resistance in our study, and future studies must incorporate drug

resistance as a potential confounder in the analysis. In Chapter 3, although we did sensitivity analysis by restricting the study population in the VACS to the first regimen used, it will be interesting to observe the change in the minimum optimal adherence threshold within a year after regimen changes. It will also be interesting to determine how adherence to specific components of the HAART regimen modify the minimum optimal adherence to HAART.

The minimum optimal adherence should be determined using other measures of adherence like MEMS cap. This form of adherence measurement although not the gold standard, has been proven more accurate than self-report and pharmacy refill records in measuring adherence in different populations.[11] Although we did not determine any significant differences in the minimum optimal adherence between self-reported adherence and adherence using pharmacy refill records, it will be interesting to evaluate changes in the minimum optimal adherence cutoff on using a relatively more accurate measure.

In the context of concomitant medication use, the impact of adherence to concomitant medications on adherence to HAART should be examined. In trying to obtain a holistic view of treatment adherence in HIV-infected persons, providers can use this knowledge to identify points of intervention and areas that will need counseling. A thorough documentation of adherence to different concomitant medications and their relationship with adherence to HAART will be a useful resource for providers. More qualitative research such as focus groups are needed to learn about patient-related behaviors that motivate adherence to non-ARV medications. Although similar work has been done by Monroe et al[8] in HIV patients with diabetes and hypertension, the

perception of different chronic non-AIDS comorbidities by patients, and how that motivated them to adhere to medications will help remedy the gap in understanding how adherence to HAART is impacted by specific chronic non-AIDS comorbidities, and their treatment.

Conclusions

With several new HAART formulations in the pipeline, research needs to constantly address previously studied issues in the light of improved formulations, as well as innovate and solve new problems associated with the treatment of HIV to fill gaps in the literature. The ultimate goal is to keep up with developments in HAART formulations, and relentlessly replenish the knowledge base regarding adherence to HAART and other treatment outcomes in the changing treatment scenario. This will guide providers of HIV care and policy-makers alike, in providing effective and safe treatment to HIV-infected persons, and maximizing and sustaining treatment benefits over a long period of time.

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Curriculum Vitae

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PERSONAL DATA

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EDUCATION

Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore, MD

PhD Candidate, Department of Epidemiology, **Expected Dec 2014**

Thesis title – "Medication Adherence in HIV-infected Adults in the Current Era of Highly Active Antiretroviral Therapy (HAART)"

Certificate in Global Health, May 2014

University of the Sciences in Philadelphia (USP), Philadelphia, PA

Master of Science in Pharmacy Administration, Jan 2008

Projects' titles – "Patient-reported outcomes measures to study the quality-of-life of psoriasis patients" and "A comparison of surgical outcomes in hospitals following Coronary Artery Bypass Graft surgery"

University of Mumbai, Mumbai, India

Bachelor of Pharmaceutical Sciences, Jun 2006

Registered Pharmacist under the Maharashtra State Pharmacy Council, India

RESEARCH EXPERIENCE

Johns Hopkins Bloomberg School of Public Health,

Research Assistant, *STATEPI,* Dept. of Epidemiology, *Jun 2011-Present*

- Designed studies, performed statistical analyses, and took the lead on manuscripts describing and evaluating adherence to HIV treatment using advanced epidemiological methods in observational cohort studies of HIV-infected persons in the United States - the Multicenter AIDS Cohort Study, and the Veterans Aging Cohort Study (through a collaboration with the VACS Coordinating Center at the VA Connecticut Healthcare System)

Center for Drug Safety and Effectiveness, Dept. of Epidemiology*, May 2012-Aug 2012*

- Researched and co-authored a study on the trends in the ambulatory diagnosis and treatment of non-malignant pain using the National Ambulatory Care Study (NAMCS)

Center to Reduce Cancer Disparities, Dept. of Epidemiology, *Jan 2011-Aug 2011*

- Conducted structured literature reviews for community-based behavioral interventions for cancer patients in the US and globally

Quintiles, *Health Outcomes Analyst*, Rockville, MD, *May 2008-Jul 2010*

Epidemiology and Outcomes Research, Late Phase Studies

- Co-authored study reports, presented at scientific meetings, and contributed to study proposals, statistical analysis plans, and project bid defense meeting preparations across several therapeutic areas through comprehensive literature reviews and writing
- As the lead medical writer for a late phase clinical trial, worked closely with the client medical writing team and collaborated with biostatisticians, clinical researchers, and project managers

UNICEF, *Research Intern*, Bihar, India, *Jun 2007-Aug 2007*

- Researched and co-authored a case study report titled: "A Study of the Accessibility of Integrated Management of Neonatal and Childhood illnesses (IMNCI) Services and Levels of Nutrition. *A Social Perspective in Rural Bihar*"

RESEARCH EXPERIENCE (continued)

- Worked in an interdisciplinary international team and conducted extensive survey research, focus group discussions, and in-depth interviews with local health officials

Novartis India Ltd.*, Intern*, Mumbai, India, *Jun 2005- Jul 2005*

- Assisted scientists in a Quality Control Laboratory with dissolution tests
- Learned details about the batch manufacturing of capsules in a manufacturing plant

TEACHING EXPERIENCE

Johns Hopkins Bloomberg School of Public Health,

Teaching Assistant, *Jun 2011-Mar 2013*

Observational Epidemiology (Jan 2013-Mar 2013)

Epidemiologic Methods- II (Oct 2012-Dec 2012)

Principles of Epidemiology (Summer Institute, 2012)

Topics in Infectious Disease Epidemiology (Summer Institute, 2011)

University of the Sciences in Philadelphia, *Teaching Assistant*, *Sep 2007-Dec 2007*

Health Economics

HONORS AND AWARDS

Delta Omega Scholarship, 2013

The Delta Omega Alpha Chapter, Johns Hopkins Bloomberg School of Public Health

The Charlotte Silverman Fund Award, 2012

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Annual Science Fair, Winner, 2004

Indian Pharmaceutical Association, Mumbai

PROFESSIONAL AFFILIATION/OTHER ACTIVITES

Universities Allied for Essential Medicines (UAEM)

Member, JHU UAEM, Nov 2011-Present

PROFESSIONAL AFFILIATION/OTHER ACTIVITES (continued)

International Society for Pharmacoepidemiology (ISPE)

Member, Special Interest Group in Adherence, Sep 2011-Present

Member, JHU-UMB Student Chapter

General Epidemiology/Methods Journal Club, JHSPH

Doctoral student coordinator, Sep 2011-May 2012

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

President, Vice-President, Member, USP Student Chapter, Sep 2006- May 2008

PEER-REVIEWED PUBLICATIONS

- **Viswanathan S**, Justice AC, Alexander GC, Brown TT, Gandhi NR, McNicholl IR, Rimland D, Rodriguez-Barradas M and Jacobson LP. Adherence and HIV RNA suppression in the current era of Highly Active Antiretroviral Therapy (HAART). Submitted to *JAIDS*. Manuscript under review.
- **Viswanathan S**, Detels R, Mehta SH, Macatangay BJ, Kirk GD and Jacobson LP. Level of adherence and HIV RNA suppression in the current era of Highly Active Antiretroviral Therapy (HAART). *AIDS and Behavior*. 2014. DOI 10.1007/s10461-014-0927-4.
- Daubresse M, Chang HY, Yu Y, **Viswanathan S**, Shah ND Stafford RS, Kruszewski SP, Alexander GC. Ambulatory diagnosis and treatment of non-malignant pain in the United States, 2000-2010. *Med Care.* 2013, 51(10):870-878
- Bharmal M, **Viswanathan S**. Late-Phase Patient Reported Outcomes. *Applied Clinical Trials*. 2009; 18 (10): 40-45

OTHER PUBLICATIONS

- Viswanathan S. Risk Factors for Multidrug Resistant Tuberculosis in Africa: A Meta-analysis. *Med J Therapeut Africa*. 2008; 1:73-79
- Viswanathan S. My UN Internship Experience. *ISPOR Connections*. 2007; 13(6): 26
- Viswanathan S. UNICEF and HIV/AIDS. *Med J Therapeut Africa*. 2007; 2:134

EDITORIAL ACTIVITIES

Peer-review activities (2012)

Archives of Internal Medicine

Pharmacotherapy

Annals of Internal Medicine

Editor-in-chief (2004)

Annual Magazine published at the MET's Institute of Pharmacy, University of Mumbai

ORAL PRESENTATIONS

- **Viswanathan S**, Detels R, Mehta SH, Macatangay BJ, Kirk GD and Jacobson LP. Changing Trend in Adherence to Highly Active Antiretroviral Therapy (HAART) and HIV RNA Suppression among HAART users in the Multicenter AIDS Cohort Study (MACS) and the AIDS Linked to Intravenous Experience (ALIVE) Study. **Oral presentation**. *9th International Conference on HIV Treatment and Prevention Adherence, Miami, FL*. June 2014. Abstract 315.
- **Viswanathan S**, Justice AC, Alexander GC, Brown TT, Gandhi NR, McNicholl IR, Rimland D, Rodriguez-Barradas M and Jacobson LP. Adherence and HIV RNA suppression in the current era of Highly Active Antiretroviral Therapy (HAART): results from the Veterans Aging Cohort Study. **Oral presentation**. *9th International Conference on HIV Treatment and Prevention Adherence, Miami, FL*. June 2014. Abstract 472.
- Adherence and HIV RNA suppression in the current era of Highly Active Antiretroviral Therapy (HAART). **Invited presentation**. *Annual Multicenter AIDS Cohort Study Meeting. Office of AIDS Research, NIH, Rockville, MD*. May 2014.
- The Effect of Concomitant Medication use on optimal adherence to HAART**.** **Invited presentation**. *Works-in-progress meeting, VA Connecticut Healthcare System*. July 2013.
- The Effect of Concomitant Medication use on optimal adherence to HAART. **Proposal seminar**. *Department of Epidemiology Seminar Series, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*. October 2012.

POSTER PRESENTATIONS

- **Viswanathan S**, Detels R, Macatangay BJC, Jacobson LP. Changing Trend in Adherence to Highly Active Antiretroviral Therapy (HAART) in the Multicenter AIDS Cohort Study. *Society for Epidemiologic Research (SER) 46th Annual Meeting, Boston, MA,* June 2013
- Bharmal M, **Viswanathan S**, Gemmen E. Monitoring of Health Economic Data in Clinical Trials. *International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 13th Annual European Congress, Prague, Czech Republic.* November 2010
- Bharmal M, **Viswanathan S**, Gemmen E. Best Practices in Reporting of Observational Studies. *ISPOR 13th Annual European Congress, Prague, Czech Republic.* November 2010
- Bharmal M, **Viswanathan S**. Treatment Satisfaction with Medication: A Review of Conceptual Framework and Applications. *ISPOR 13th Annual European Congress, Prague, Czech Republic.* November 2010
- **Viswanathan S**, Bharmal M, Gemmen E. Health-related Quality-of-Life Among Women with Coronary Artery Disease Treated with Psychotropic Medications. *ISPOR 15th Annual Meeting, Atlanta, GA, USA.* May 2010
- Bharmal M, **Viswanathan S**, Jo H, Garvert W, Gemmen E. Health-Related Quality-of-Life Among Elderly Patients Using Potentially Inappropriate Medications. *International Society for Quality of Life Research 16th Annual Meeting, New Orleans, LA, USA.* October 2009
- **Viswanathan S**, Gemmen E, Bharmal M. Evaluating Central Nervous System Drug Labels for Patient-Reported Outcomes Claims. *ISPOR 14th Annual Meeting, Orlando, FL, USA.* May 2009
- **Viswanathan S**, Neville W, Patel E, Raparla S, McGhan WF. A Cost-Effectiveness Model for Smoking Cessation Therapy using Varenicline. *ISPOR 13th Annual Meeting, Toronto, Canada.* May 2008
- **Viswanathan S**, McGhan WF. A Cost-Effectiveness Analysis of TNF-α Inhibitors in Comparison to Other Strategies in the Treatment of Psoriasis: A Decision Analytic model. *ISPOR 13th Annual Meeting, Toronto, Canada.* May 2008

POSTER PRESENTATIONS (continued)

- McGhan WF, Tundia N, Quadri H, **Viswanathan S**, and Peterson AM. Evaluating an Online Calculator for Analyzing Incremental Net Benefit and the Expected Value of Perfect Information from Patient Level Data. *ISPOR 12th Annual Meeting, Arlington, VA, USA*. May 2007